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Management of Chronic Hepatitis C

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Structured Abstract

Objectives Hepatitis C is the most common blood-borne infection in the United States and can lead to serious complications including cirrhosis and hepatocellular carcinoma (HCC). The objectives of this report are to summarize evidence on the following questions in the management of chronic hepatitis C: How well do results of liver biopsy predict outcomes of treatment for chronic hepatitis C? How well do biochemical blood tests and serologic measures of fibrosis predict the findings of liver biopsy in chronic hepatitis C? What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients and in selected subgroups? What are the long-term outcomes of current treatment options for chronic hepatitis C? What is the efficacy of using screening tests for HCC to improve outcomes in chronic hepatitis C? What are the sensitivity and specificity of tests used to screen for HCC in chronic hepatitis C?

Search strategy Eight electronic databases were searched for the period between January 1996 to March 2002. Additional articles were identified by searching for references in pertinent articles and current relevant journals and by querying technical experts.

Selection criteria Articles were eligible for review if they reported original human data from a study that was designed to address a key question and that used virologic, histologic, pathologic, or clinical outcome measures. Each question had additional eligibility criteria.

Data collection and analysis Paired reviewers assessed the quality of each eligible study and abstracted data. Data were assembled in evidence tables to facilitate synthesis.

Main results For the six questions investigated, the results are as follows: 1) studies were relatively consistent in suggesting that advanced fibrosis or cirrhosis on initial liver biopsy may be an independent predictor of a slightly decreased likelihood of having a sustained virological response to treatment; 2) studies were relatively consistent in showing that serum liver enzymes have modest value in predicting fibrosis on biopsy; the extracellular matrix tests, hyaluronic acid and laminin, may have value in predicting fibrosis, and panels of tests may have the greatest value in predicting fibrosis or cirrhosis; 3) studies of treatment-naive patients with chronic hepatitis C showed greater efficacy of pegylated (peg) interferon plus ribavirin when compared to standard interferon plus ribavirin or peginterferon alone, greater efficacy of peginterferon when compared to standard interferon, and no significant increase in efficacy with standard interferon plus amantadine when compared to interferon monotherapy; for nonresponders and relapsers, standard interferon plus ribavarin was more efficacious than interferon alone; little evidence existed on treatment efficacy in HIV-infected patients, renal patients, hemophiliacs, or intravenous drug users; 4) studies were mildly consistent in suggesting that interferon-based therapies decrease the risk of HCC and cirrhosis in complete responders; 5) one study suggested that HCC was detected earlier and was more often resectable in patients who had quarterly screening with serum alpha-fetoprotein (AFP) and ultrasound than in those who had usual care; 6) studies were relatively consistent in suggesting that a serum AFP greater than 10 ng/mL has a

sensitivity of 75 to 80 percent and a specificity of about 95 percent in screening for HCC, and a serum AFP greater than 400 ng/mL has a specificity of nearly 100 percent for detection of HCC.

Conclusions The evidence suggests that liver biopsy may have some usefulness in predicting the efficacy of treatment in patients with chronic hepatitis C, and that biochemical blood tests and serologic tests have modest value in predicting the results of liver biopsy. The most efficacious treatment for chronic hepatitis C is peginterferon plus ribavirin; however few studies have examined treatment efficacy in injection drug users and those co-infected with HIV. Screening for HCC with AFP and ultrasound may improve outcomes, but studies are needed to identify the optimal screening strategy.

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Summary

Overview

Hepatitis C, a viral disease, is the most common blood-borne infection in the United States, affecting more than 4 million Americans. Approximately 36,000 cases of acute hepatitis C infection occur each year in the United States and 85 percent of those with acute hepatitis C develop a chronic infection. Chronic hepatitis C is often asymptomatic but may lead to cirrhosis of the liver as well as hepatocellular carcinoma (HCC). The natural history is variable, and progression to cirrhosis is estimated to occur in approximately 20 percent of patients. Prognosis of those with hepatitis C-related cirrhosis often depends on the development of hepatic decompensation or HCC. The 10-year survival of those with chronic hepatitis C is approximately 50 percent for those with uncomplicated cirrhosis and the median survival for HCC is approximately 6-20 months. Chronic hepatitis C is the leading cause of liver transplants and HCC in the United States and accounts for between 8,000 and 10,000 deaths per year. Without advances in treatment, the number of deaths could triple in the next 10 to 20 years.

The National Institutes of Health (NIH) conducted a Consensus Development Conference in 1997 on the management of hepatitis C. Missing from the conclusions and recommendations of the 1997 conference was discussion of the utility of liver biopsy in determining the appropriateness of treatment or the best protocols for screening for hepatocellular carcinoma. In addition, medical research has made significant progress in the past 5 years regarding treatment modalities for chronic hepatitis C, with pegylated (peg) interferon and ribavirin showing promising results. Recent research has shown that certain subgroups of patients may be more or less likely to benefit from treatment based on clinical factors such as ethnicity, hepatitis C virus (HCV) genotype, or initial response to therapy. In addition, a substantial number of patients treated with initial therapies either relapsed after treatment or never responded. The NIH is convening another Consensus Development Conference on the management of hepatitis C to update the recommendations on prevention, diagnosis, and treatment of hepatitis C. The purpose of this Evidence Report is to review and synthesize the recent literature on several key questions on the management of chronic hepatitis C that will be addressed at the Consensus Development Conference.

Reporting the Evidence

This report addresses the following key questions in the management of chronic hepatitis C.

Role of Initial Liver Biopsy

- **Q1b: How well do the results of initial liver biopsy predict outcomes of treatment in patients with chronic hepatitis C, taking into consideration patient characteristics such as viral genotype?**

  Initial biopsy means the biopsy that occurs at initial evaluation before treatment decisions are made. The main outcomes of interest were virologic and histologic measures of disease activity and progression.

- **Q1e: How well do biochemical blood tests and serologic measures of fibrosis predict the findings of liver biopsy in patients with chronic hepatitis C?**

  The focus was on biochemical and serologic tests that clinicians could use to estimate the likelihood of fibrosis in patients with chronic hepatitis C.

Treatment Options

- **Q2a: What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients, including: peginterferon plus ribavirin, peginterferon alone, standard interferon plus ribavirin, and standard interferon plus amantadine?**

  Efficacy was assessed in terms of virologic and histologic response to treatment as well as other clinical outcomes including the incidence of cirrhosis, hepatic decompensation, HCC, death, and adverse effects of treatment.

- **Q2c: What is the efficacy and safety of current interferon-based treatment options (including interferon alone) for chronic hepatitis C in selected subgroups of patients, especially those defined by the following characteristics: age less than or equal to 18 years, race/ethnicity, HCV genotype, presence or absence of cirrhosis, minimal versus decompensated liver disease, concurrent hepatitis B or HIV infection, nonresponse to initial interferon-based therapy, and relapse after initial interferon-based therapy?**

  Efficacy was assessed in terms of virologic and histologic response to treatment as well as other clinical outcomes.

- **Q2d: What are the long-term clinical outcomes (greater than or equal to 5 years) of current treatment options for chronic hepatitis C?**

  The main outcomes of interest were the incidence of cirrhosis, hepatic decompensation, HCC, and death. This question included studies of the natural history of chronic hepatitis C because observation is an option.

Screening for Hepatocellular Carcinoma

- **Q3a: What is the efficacy of using screening tests for hepatocellular carcinoma to improve clinical outcomes in patients with chronic hepatitis C?**

  The review on this question focused on alpha-fetoprotein, other serological markers, ultrasonography, computerized tomography, and other imaging studies. The outcomes of interest were mortality and the rate of resectable versus nonresectable HCC.

- **Q3b: What are the sensitivity, specificity, and predictive values of tests that could be used to screen for hepatocellular carcinoma (especially resectable carcinoma) in patients with chronic hepatitis C?**

  The review on this question focused on the same screening tests listed above.

Methodology

The Evidence-based Practice Center (EPC) team recruited 20 technical and community experts to provide input into the definition of the key questions and to review a draft of the report. These included hepatitis specialists from academic settings and experts from relevant professional organizations and other settings. The EPC team also recruited representatives from a range of other stakeholder organizations to serve as peer reviewers of the draft Evidence Report. The reviewers included an allied health professional, experts in assessment of diagnostic technologies, and other clinical specialists drawn from academic and government settings.

Several literature sources were used to identify all studies potentially relevant to the research questions. Eight electronic databases were searched through DIALOG (a commercial database vendor) for the period from January 1, 1996 to September 30, 2001: MEDLINE®; Biological Abstracts-BIOSIS Previews®; Science Citation Index-SciSearch®; Manual, Alternative and Natural Therapy-MANTIS; the Allied and Complementary Medicine Database; CAB Health; PsycINFO; and Sociological Abstracts. To ensure a comprehensive literature search and identification of all relevant articles, the EPC team updated the search in March 2002, examined the reference lists from material identified through the electronic searching and discussion with experts, and reviewed the tables of contents of recent issues of journals that were cited most frequently (between October 2001 and March 2002).

Two members of the study team independently reviewed the titles and abstracts identified by the search to exclude those that did not meet the following eligibility criteria: 1) written in English; 2) includes human data; 3) original data; 4) information relevant to the management of hepatitis C; 5) reports basic sciences as well as clinical data; 6) applies to one of the key questions. Also excluded were meeting abstracts (no full article for review). Citations deemed not relevant by both reviewers were excluded. To focus the search on the studies that would be most valuable in addressing the key questions, the following types of studies were excluded: 1) studies in which all data was reported in a subsequent publication; 2) studies that may have contained some data related to a key question but the study was not designed to address the question; 3) studies that addressed management of hepatitis C in liver transplant patients only; 4) studies in which the total number of participants was less than 30; and 5) studies in which the outcomes/results were not measured with an appropriate objective standard (i.e., virologic and/or histologic measures of treatment response, or histologic or pathologic evidence of HCC for the screening questions).

Focus of Key Questions

For key question 1b, we included only randomized controlled trials because they provide the strongest evidence on whether the findings on initial liver biopsy are independent predictors of the greater efficacy of one treatment strategy compared to another. Although cohort studies could provide evidence of the relation between initial histology and the response to a given treatment regimen, they are susceptible to selection bias because patients could be excluded from a cohort on the basis of histological findings. We also required at least 24 weeks of follow-up for key question 1b.

For key question 1e, we included only studies that evaluated biochemical blood tests or serological tests that could serve as measures of liver fibrosis. These studies could include other tests, but we did not include studies that examined only other tests such as hematologic tests or radiologic imaging studies.

For key questions 2a and 2c, we included only randomized controlled trials that had a planned length of follow-up that was at least 24 weeks after the end of treatment.

For key question 2d, we included only studies that had at least 5 years of follow-up, including studies of natural history without treatment.

For key question 3a, we looked for studies on patients with chronic hepatitis C that had at least 6 months of follow-up for comparing one screening strategy to another screening strategy or to no screening.

For key question 3b, we included only studies that reported data on patients with hepatitis C although these studies could include some patients with only hepatitis B or patients co-infected with HCV and hepatitis B virus (HBV). We excluded studies that focused solely on hepatitis B because the pathophysiology and natural history of hepatitis C differs from that of hepatitis B.

Review Process

Paired reviewers assessed the quality of each eligible study in terms of representativeness of the study population (5 items), bias and confounding (4 items), description of therapy/management (4 items), outcomes and follow-up (5 items), and statistical quality and interpretation (4 items). The score for each category of study quality was the percentage of the total points available in each category for that study and could range from zero to 100 percent. The total quality score was the average of the five categorical scores. In addition, the reviewers also completed an item on potential conflict of interest. At least one reviewer in a pair had clinical training and at least one reviewer had training in epidemiology and clinical research methods. One reviewer in the pair was responsible for completing both the quality assessment and content abstraction, and the second reviewed and confirmed the material abstracted.

Findings

Q1b: How well do the results of initial liver biopsy predict outcomes of treatment in patients with chronic hepatitis C, taking into consideration patient characteristics such as viral genotype?

- A moderate number of randomized controlled trials addressed this question.
- These studies varied widely in how they reported the relation of initial histological findings to the outcomes of treatment.
- The analyses for this question had important limitations including frequent lack of reporting of parameter estimates and confidence intervals.
- The studies that used multivariate analysis were relatively but not entirely consistent in suggesting that the presence of advanced fibrosis or cirrhosis on initial liver biopsy may predict a modest decrease in the likelihood of having a sustained virological response to treatment. The studies suggested that there is no interaction between pre-treatment liver histology and the effect of different treatment regimens on the rate of sustained virological response.

Q1e: How well do biochemical blood tests and serologic measures of fibrosis predict the findings of liver biopsy in patients with chronic hepatitis C?

- Numerous studies evaluated the value of biochemical tests and serologic measures of fibrosis in predicting fibrosis on liver biopsy in chronic hepatitis C.
- The studies had some important limitations and varied widely in published evidence: they covered numerous tests and used a variety of methods for reporting results.
- The studies were relatively consistent in showing that 1) serum liver enzymes have only modest value in predicting fibrosis on liver biopsy, 2) the extracellular matrix tests hyaluronic acid and laminin have modest value in predicting fibrosis on liver biopsy, 3) cytokines have less value than the extracellular matrix tests in predicting fibrosis on liver biopsy, and 4) panels of tests may have the greatest value in predicting the absence of more than minimal fibrosis on liver biopsy and in predicting the presence versus absence of cirrhosis on biopsy.

Q2a: What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients, including peginterferon plus ribavirin, peginterferon alone, standard interferon plus ribavirin, and standard interferon plus amantadine?

Peginterferon Plus Ribavirin

- Two published trials evaluated the efficacy of peginterferon plus ribavirin for the treatment of

hepatitis C. The results of an additional large trial have not yet been published.

- The largest of these two trials had a relatively high score in all five categories of study quality, but generalizability was limited by the exclusion of patients with HIV infection, previous interferon treatment, mental illness, or other significant co-morbidity (among other exclusions).
- The studies were consistent in showing a significant increase in efficacy with peginterferon plus ribavirin compared with standard interferon plus ribavirin or peginterferon alone.

Peginterferon Alone

- A few randomized controlled trials evaluated the efficacy of standard peginterferon alone for the treatment of chronic hepatitis C.
- The studies had relatively high study quality scores, but differed significantly in the distribution of patients by race/ethnicity, HCV genotype, and presence of cirrhosis.
- The studies were somewhat consistent in showing a large relative increase in virological sustained response and a modest increase in histological response with peginterferon compared with standard interferon.

Standard Interferon Plus Ribavirin

- A large number of trials evaluated the efficacy of standard interferon and ribavirin therapy for the treatment of hepatitis C.
- A previous systematic review demonstrated an increased efficacy of standard interferon plus ribavirin compared with standard interferon alone in treatment-naive patients.
- The additional studies reviewed were somewhat consistent in showing at least a modest increase in virological sustained response with standard interferon plus ribavirin compared with standard interferon alone.
- The magnitude of the relative treatment effect may depend on the dose and duration of treatment as each study used a different treatment regimen.

Standard Interferon Plus Amantadine

- A moderate number of trials evaluated the efficacy of standard interferon plus amantadine therapy for the treatment of chronic hepatitis C.
- Evidence on the efficacy of standard interferon and amantadine was fairly homogeneous with relatively high study quality scores and some variation in treatment protocols.
- The studies were relatively consistent in showing that standard interferon plus amantadine is not more effective than standard interferon monotherapy and is not more effective than standard interferon plus ribavirin in treatment-naive patients.

Q2c: What is the efficacy and safety of current interferon-based treatment options (including interferon alone) for chronic hepatitis C in selected subgroups of patients, especially those defined by the following characteristics: age less than or equal to 18 years, HCV genotype, presence or absence of cirrhosis, minimal versus decompensated liver disease, concurrent hepatitis B or HIV infection, nonresponse to initial interferon-based therapy, and relapse after initial interferon-based therapy?

Standard Interferon Plus Ribavirin: Relapsers and Nonresponders

- A moderate number of trials evaluated the efficacy of standard interferon plus ribavirin for the treatment of chronic hepatitis C in patients who previously failed to respond to interferon or who relapsed after interferon treatment.
- Evidence of the efficacy of standard interferon plus ribavirin in nonresponders is heterogeneous and has methodologic limitations including differences in HCV genotype, gender, and treatment protocols among the studies.
- Efficacy data was stronger for sustained virological response than for clinical outcomes like cirrhosis and hepatitis C specific mortality.
- Previous systematic reviews suggested a small but significant increase in sustained virological response in nonresponders receiving combination therapy with standard interferon plus ribavirin.
- The additional studies reviewed were consistent in showing combination therapy has greater efficacy than standard interferon monotherapy in improving end-of-treatment response in nonresponders; however, this response was not consistently sustained through follow-up.
- Evidence of the efficacy of standard interferon plus ribavirin in relapsers and nonresponders combined was heterogeneous and had methodologic limitations.
- A previous systematic review reported that this type of combination therapy had a greater efficacy than standard interferon monotherapy for relapsers and nonresponders combined.
- The additional studies reviewed were relatively consistent in demonstrating that longer duration of interferon and ribavirin therapy has a greater efficacy than shorter duration in both interferon relapsers and nonresponders. Furthermore, the evidence was consistent in showing that

interferon relapsers have a better response to therapy than previous nonresponders.

Standard Interferon Plus Amantadine

- Two studies evaluated the efficacy of standard interferon plus amantadine for treatment of chronic hepatitis C in patients who did not respond to previous interferon treatment. These studies were small but one had a high study quality score.
- The studies suggested that amantadine plus standard interferon is not more effective than standard interferon alone.
- Only one small study evaluated the efficacy of standard interferon in combination with ribavirin and amantadine compared to interferon and ribavirin in nonresponders.

Interferon Monotherapy

- A moderate number of studies evaluated the efficacy of standard interferon therapy for the treatment of chronic hepatitis C in selected subgroups of clinical interest.
- The evidence of the efficacy of standard interferon in specific clinical subgroups is heterogeneous and had important limitations.
- Few randomized controlled trials of standard interferon therapy focused on HIV-infected patients, renal patients, hemophiliacs, or intravenous drug users.
- The studies that have been done were consistent in showing that standard interferon monotherapy is relatively ineffective in the retreatment of nonresponders and relapsers.

Q2d: What are the long-term clinical outcomes (greater than or equal to 5 years) of current treatment options for chronic hepatitis C?

Interferon-treated Patients

- The evidence of the effect of interferon-based therapy on long-term outcomes in hepatitis C is heterogeneous and has important methodologic limitations, including variable lengths of follow-up within and among studies, variable numbers of patients with cirrhosis, different doses and durations of therapy (and this information is frequently missing), varying amounts of alcohol consumption, and little description of the population that was not treated.
- These studies were nonetheless somewhat consistent in suggesting that treatment with interferon-based therapy decreases the risk of HCC and cirrhosis in complete responders.
- The evidence also suggested that biochemical responders may also have a decreased risk of HCC and decreased progression of liver disease.
- The data were inconsistent regarding the impact of interferon therapy in nonresponders and relapsers compared with each other and with untreated controls. One long-term randomized trial suggested that all patients treated with interferon, regardless of response, derive long-term benefits; other studies suggested that relapsers but not nonresponders or controls derive long-term benefit from interferon therapy.

Natural History

- The evidence on the natural history of hepatitis C is very heterogeneous and has important methodologic limitations. The studies, however, were consistent in suggesting that older age, cirrhosis, hepatitis B coinfection, HIV infection, alcoholism, male sex, and initial fibrosis all predict worse long-term outcomes in hepatitis C.
- The studies were somewhat consistent in showing that HCV genotype does not increase the rate of fibrosis progression in patients with chronic hepatitis C.
- Studies were somewhat consistent in showing that HBV coinfection hastens the progression of liver disease in patients with chronic hepatitis C.
- Studies were consistent in showing that patients with chronic hepatitis C who have a normal ALT have a lower incidence of HCC at 5 years.

Q3a: What is the efficacy of using screening tests for hepatocellular carcinoma to improve clinical outcomes in patients with chronic hepatitis C?

- Only one prospective cohort study and no randomized controlled trials evaluated the efficacy of screening for HCC in patients with chronic hepatitis C.
- The prospective cohort study had important limitations, especially the fact that it included patients with chronic liver disease—primarily due to hepatitis B or C, but also due to other causes—and thus may not be representative of the development of HCC in patients with hepatitis C.
- This study suggested that HCC was detected earlier and was more often resectable in patients who underwent routine screening with AFP and hepatic ultrasound than in those who had usual care.

Q3b: What are the sensitivity, specificity, and predictive values of tests that could be used to screen for hepatocellular carcinoma (especially resectable carcinoma) in patients with chronic hepatitis C?

- Numerous trials evaluated the performance characteristics of serum AFP in screening for HCC in patients with chronic hepatitis C.
- These studies had important methodologic weaknesses and varied widely in study design and patient eligibility criteria.

- The studies were relatively consistent in suggesting that a serum AFP level of greater than 10 ng/mL has a moderate sensitivity of 75 to 80 percent and a specificity of approximately 95 percent in screening for HCC, and that a serum AFP level of greater than 400 ng/mL has a low sensitivity with a specificity of nearly 100 percent.
- Several other serologic and urinary screening tests have been evaluated, but none of these has been evaluated in more than two studies.
- Few of these studies had a large enough population of patients with chronic hepatitis C to provide reliable estimates of the performance characteristics of the tests.
- The studies on use of soluble interleukin-2 receptor level and protein induced in vitamin K absence (PIVKA-II) suggested that these tests could be useful in screening for HCC if combined with serum AFP or ultrasonography.
- A few studies evaluated the performance characteristics of ultrasonography in screening patients with hepatitis C.
- These studies had some limitations in that they varied by screening frequency, experience of the ultrasonographer, and extent of liver disease in the screened patients.
- The studies using ultrasonography were relatively consistent in demonstrating high specificity but variable sensitivity depending on the population screened.
- Combination screening with AFP and ultrasonography demonstrated an increase in sensitivity in at least one trial of patients with hepatitis B or C.
- Two studies reported on the performance characteristics of computerized tomography and magnetic resonance imaging.
- These studies were limited in that they were not designed to assess the efficacy of screening, but to evaluate the incidence of HCC.
- The studies were consistent, however, in demonstrating both a high sensitivity and specificity in patients with hepatitis C.

Future Research

Relation of Initial Liver Biopsy Findings to Outcomes of Treatment

Future treatment studies need to be designed to appropriately answer this question using initial liver biopsy findings in analysis of factors associated with a virologic or histologic response to therapy. These studies should use standard techniques for obtaining adequate liver biopsy samples and standardized reporting of liver biopsy results. The studies also should report the details of both univariate and multivariate analyses of the relation of initial biopsy findings to outcomes, including adjusted and unadjusted parameter estimates of the relation of each histological variable to the outcome variable, and whether the analysis considered potential interaction effects. Such studies would help to provide better estimates of the independent value of liver biopsy in predicting outcomes of treatment options.

Tests to Predict Fibrosis on Liver Biopsy

Future studies will need to be designed to more directly address this question. Such studies should give attention to the methodologic limitations we encountered in trying to extract meaningful information from the studies performed to date. In particular, the studies should provide enough details about the liver biopsy methods to convince readers of the adequacy of the reference standard. Future studies also should give more attention to the potential value of a panel of tests for predicting fibrosis on liver biopsy.

Treatment of Chronic Hepatitis C

Future studies will need to further address the questions of the optimal doses and duration of therapies. In addition, randomized controlled trials should include traditionally understudied populations with high rates of hepatitis C, such as blacks, injection drug users, alcoholics, and those with renal disease or HIV. In particular, randomized controlled trials of treatments for chronic hepatitis C should include subgroup analysis by gender and race/ethnicity, as some studies have suggested different response rates between women and men, and between different racial/ethnic groups. Such studies should give attention to the methodologic limitations we encountered in trying to extract meaningful information from the studies performed to date.

Long-term Outcomes of Chronic Hepatitis C

Future studies will need to assess the long-term outcomes of current treatment options, particularly studies with standard interferon plus ribavirin, as well as new studies with peginterferon. Although some data has suggested that longer treatment is better for improving virologic outcomes, little is known regarding the long-term outcomes of different treatment durations. Finally, although natural history studies may no longer be practical in the current treatment era, following certain subgroups at high risk for complications, such as patients co-infected with HIV or HBV, injection drug users, and alcoholics, will be useful in making clinical recommendations regarding follow-up for these patients.

Efficacy of Screening for HCC

Randomized controlled trials of screening of patients with hepatitis C will be most useful in helping to determine screening recommendations for these patients; however, it is difficult to conduct large, randomized controlled trials of

screening strategies. Therefore, conducting trials on the patients at greatest risk may yield the most significant results. At the present time, serum AFP and ultrasonography appear to hold the most promise.

Performance Characteristics of Screening Tests

Future studies should include randomized controlled trials of screening for HCC in patients with chronic hepatitis C. Although it may be difficult to conduct randomized controlled trials in all patients with hepatitis C, including patients at highest risk for HCC in screening trials makes it more likely that future research will determine definitively the benefits of screening. Future studies should consider the use of a combination of screening tests and should consider examining the relative cost-effectiveness of alternative strategies.

Future studies also should consider examining promising new tests such as soluble Interleukin-2 receptor compared to and possibly combined with the currently most sensitive screening options, including serum AFP and ultrasonography.

Overall Areas of Future Research

Most studies reviewed provided limited information on the type and degree of involvement of the funding source. Consistent with new reporting guidelines accepted by many major journals, this information should become part of the standard data report in future trials.

In addition, to improve the quality of publications on these study questions, standardized methods should be developed and disseminated to investigators. Journals should encourage standardized approaches to presenting data on these questions. For published articles, full copies of protocols should be made available, perhaps on the Web. This is important because the pressure to shorten manuscripts often results in reduced descriptions of study methods.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Johns Hopkins University Evidence-based Practice Center, Baltimore, MD, under contract number 290-97-0006. It is expected to be available in summer 2002. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 60, *Management of Chronic Hepatitis C*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1: Introduction

Hepatitis C, a viral disease, is the most common blood-borne infection in the United States. According to the Centers for Disease Control and Prevention (CDC), approximately 36,000 cases of acute hepatitis C infection occur each year in the United States. Approximately 85 percent of those with acute hepatitis C develop a chronic infection.[1,2] Chronic hepatitis C is often asymptomatic but may cause progressive liver injury. The hepatitis C virus (HCV) infects over 170 million persons worldwide and over 4 million Americans.[1] Chronic hepatitis C has significant morbidity and mortality as it can lead to cirrhosis of the liver as well as hepatocellular carcinoma (HCC).

Approximately 15 to 25 percent of patients with chronic hepatitis C develop cirrhosis.[3,4] The time frame between infection and development of cirrhosis is affected by several factors including use of alcohol[5] and viral co-infection with HIV or hepatitis B[6-8] male sex, and older age at infection.[9-11] The prognosis of those with HCV-related cirrhosis often depends on development of two complications, hepatic decompensation and HCC. The 10-year survival of those with chronic hepatitis C is approximately 50 percent for those with uncomplicated cirrhosis.

Chronic hepatitis C is the leading cause of liver transplants and HCC in the United States, and it accounts for between 8,000 and 10,000 deaths per year. Without advances in treatment, the number of deaths could triple in the next 10 to 20 years.

The National Institutes of Health (NIH) conducted a Consensus Development Conference in 1997 regarding the management of hepatitis C. The Conference addressed several important questions on prevention, diagnosis, and management of hepatitis C. The conclusions of the 1997 Consensus Development Conference were as follows:

"Hepatitis C is a common infection with variable course that can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The course of illness may be adversely affected by various factors, especially alcohol consumption. Therefore, more than one drink per day is strongly discouraged in patients with hepatitis C, and abstinence from alcohol is recommended. Initial therapy with interferon alfa (or equivalent) should be 3 million units three times per week for 12 months. Patients not responding to therapy after 3 months should not receive further treatment with interferon alone, but should be considered for combination therapy of interferon and ribavirin or for enrollment in investigational studies. Individuals infected with the hepatitis C virus should not donate blood, organs, tissues, or semen. Safe sexual practices, including the use of latex condoms, are strongly encouraged for individuals with multiple sexual partners. Expansion of needle exchange programs should be considered in an effort to reduce the rate of transmission of hepatitis C among injection drug users."[3]

Notably missing from the conclusions and recommendations is discussion of the utility of liver biopsy in determining the appropriateness of treatment or the best protocols for screening for hepatocellular carcinoma. Medical research has made significant progress in the past 5 years regarding treatment modalities for chronic hepatitis C, with peginterferon[12,13] showing promising results. In addition, research has shown that certain subgroups of patients may be more or less likely to benefit from treatment based on clinical factors such as ethnicity, HCV genotype, or initial response to therapy. In addition, a substantial number of patients treated with

initial therapies have either relapsed after treatment or never responded. The future treatment of these patients needs to be explored further.

In 2002, the National Institutes of Health will convene another Consensus Development Conference on the management of hepatitis C. The purpose of this conference will be to determine the state of the art regarding several questions:

- What is the natural history of hepatitis C?
- What is the most appropriate approach to diagnosis and monitoring of patients with chronic hepatitis C?
- What is the most effective therapy for hepatitis C?
- Which patients with hepatitis C should be treated?
- What recommendations can be made to patients to prevent transmission of hepatitis C?
- What are the most important areas for future research?[14]

To this end, the Johns Hopkins University Evidence-based Practice Center (JHU EPC) prepared this evidence report focusing on several key questions on the management of chronic hepatitis C that warranted a systematic review of the recent literature. The EPC intended for this evidence report to be a resource for the Consensus Development Conference Panel that will formulate recommendations regarding the management of hepatitis C. The report should also be a resource for clinicians and policy makers who must make decisions about management of patients with chronic hepatitis C.

Chapter 2: Methodology

Recruitment of Experts

The EPC team identified a core group of 20 technical and community experts to provide input at key points during the project (see Appendix A). These included hepatitis specialists and other experts drawn from academic settings, from relevant professional organizations, and other settings.

The experts from relevant professional organizations were drawn from the American Association for the Study of Liver Diseases, the American College of Physicians-American Society of Internal Medicine, the Infectious Disease Society of America, and the American Academy of Pediatrics. In addition, there was an expert in the assessment of diagnostic technologies and a representative from the Centers for Medicare and Medicaid Services.

The EPC team also identified representatives from a range of other stakeholder organizations to serve as peer reviewers of the draft Evidence Report. The reviewers included an allied health professional, another expert in the assessment of diagnostic technologies, and other clinical specialists drawn from academic and governmental settings (see Appendix A).

The EPC team involved the core experts in defining the key questions (see Identifying the Specific Questions, below) and asked both experts and peer reviewers to review the draft report (see Peer Review Process, below).

Target Population

The targeted clinical population consisted of patients with chronic hepatitis C. The main targeted users of the report are members of the expert panel that is responsible for formulating the consensus statement of the NIH Consensus Development Conference on Management of Hepatitis C in June 2002. This report also should be of interest to clinicians treating HCV-infected patients.

Identifying the Specific Questions

In July 2001, representatives of the EPC team attended the meeting of the Consensus Development Conference Planning Committee that was appointed by the NIH Office of Medical Applications of Research (OMAR). At this meeting the Planning Committee discussed the questions that should be addressed in the Consensus Development Conference and decided on the questions that warranted a systematic review of the literature. The EPC team then formulated these key questions in specific terms that would focus the review process on the most relevant published studies. The EPC team carried out preliminary literature searches and on the basis of those results further refined the key questions. The proposed questions were sent to the core technical experts to rate their relevance and importance. Reviewers commented on the clarity of each question and the availability of evidence to answer it. The EPC team reviewed the experts'

ratings and comments and established the final list of key questions that would be addressed in the Evidence Report.

Key Questions

The EPC team sought to address the following key questions as they pertained to management of chronic hepatitis C.

Role of Initial Liver Biopsy

Q1b: How well do the results of initial liver biopsy predict outcomes of treatment in patients with chronic hepatitis C, taking into consideration patient characteristics such as viral genotype?

Initial biopsy means the biopsy that occurs at initial evaluation before treatment decisions are made. The main outcomes of interest are virologic and histologic measures of disease activity and progression.

Q1e: How well do biochemical blood tests and serologic measures of fibrosis predict the findings of liver biopsy in patients with chronic hepatitis C?

We were interested primarily in biochemical and serologic tests that clinicians could use to estimate the likelihood of fibrosis in patients with chronic hepatitis C. Such information could help guide clinical decisions about the need for an initial liver biopsy.

Treatment Options

Q2a: What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients, including peginterferon plus ribavirin, peginterferon alone, standard interferon plus ribavirin, and standard interferon plus amantadine?

Efficacy was assessed in terms of virologic and histologic response to treatment as well as other clinical outcomes including the incidence of cirrhosis, hepatic decompensation, HCC, death, and adverse effects of treatment.

Q2c: What is the efficacy and safety of current interferon-based treatment options (including interferon alone) for chronic hepatitis C in selected subgroups of patients, especially those defined by the following characteristics: age less than or equal to 18 years, race/ethnicity, HCV genotype, presence or absence of cirrhosis, minimal versus decompensated liver disease, concurrent hepatitis B or HIV infection, nonresponse to initial interferon-based therapy, and relapse after initial interferon-based therapy?

Efficacy was assessed in terms of virologic and histologic response to treatment as well as other clinical outcomes including the incidence of cirrhosis, hepatic decompensation, HCC, death, and adverse effects of treatment.

Q2d: What are the long-term clinical outcomes (greater than or equal to 5 years) of current treatment options for chronic hepatitis C?

The main outcomes of interest were the incidence of cirrhosis, hepatic decompensation, HCC, and death. This question included studies of the natural history of chronic hepatitis C because observation is an option.

Screening for Hepatocellular Carcinoma

Q3a: What is the efficacy of using screening tests for hepatocellular carcinoma to improve clinical outcomes in patients with chronic hepatitis C?

The review on this question focused on the following tests: alpha fetoprotein, other serological markers, ultrasonography, computerized tomography, and other imaging studies. The main outcomes of interest were mortality and the rate of resectable versus nonresectable HCC.

Q3b: What are the sensitivity, specificity, and predictive values of tests that could be used to screen for hepatocellular carcinoma (especially resectable carcinoma) in patients with chronic hepatitis C?

The review on this question focused on the same screening tests listed under question 3a.

Causal Pathway

To show how the key questions relate to the overall management of patients with chronic hepatitis C, the EPC team developed a description of a causal pathway (Figure 1). The causal pathway depicts patient characteristics and the types of outcomes that need to be considered in management decisions. The pathway also provides a conceptual framework for identifying gaps in our knowledge about management of chronic hepatitis C.

Literature Search Methods

The literature search consisted of several steps, including identifying sources, formulating a search strategy for each source, and executing and documenting each search. The literature search was conducted through DIALOG, a commercial database vendor, by which each database was searched and the results combined to identify duplicate citations through the DIALOG duplicate checker. This process which delivers a consolidated and nonduplicated list of references, is an economical approach to database searching since the DIALOG system pricing is based on the number of citations downloaded or printed.

Sources

Several literature sources were used to identify all studies potentially relevant to the research questions. Both electronic database searching and manual searching was performed. Eight electronic databases were searched through DIALOG for the period from January 1, 1996 to September 30, 2001. An updated search was completed in March, 2002. The databases

searched are described below. For the key questions that were not addressed at the 1997 Consensus Development conference (i.e., questions 1b, 1e, 3a, and 3b), we also searched MEDLINE® back to 1985.

MEDLINE®

MEDLINE®, or MEDLARS® on-line, is a database of bibliographic citations and author abstracts from approximately 3,900 current biomedical journals published in the United States and 70 foreign countries, dating back to 1966. MEDLINE® was accessed through PubMed, the Internet access to MEDLINE® provided by the National Library of Medicine (NLM).

Biological Abstracts - BIOSIS Previews®

Biosis previews contains citations from *Biological Abstracts*® (BA) and *Biological Abstracts/Reports, Reviews, and Meetings*® (BA/RRM) (formerly *BioResearch Index*®), the major publications of BIOSIS®. Together, these publications constitute the major English-language service providing comprehensive worldwide coverage of research in the biological and biomedical sciences. *Biological Abstracts* includes approximately 350,000 accounts of original research yearly from nearly 6,000 primary journal and monograph titles. *Biological Abstracts/RRM* includes an additional 200,000 citations a year from meeting abstracts, reviews, books, book chapters, notes, letters, selected institutional and government reports, and research communications. U.S. patents are included from 1986 through 1989.

Science Citation Index - SciSearch®

Science citation Index-Sci Search is an international, multidisciplinary index to the literature of science, technology, biomedicine, and related disciplines produced by the Institute for Scientific Information® (ISI®). SciSearch contains all of the records published in the Science Citation Index®, plus additional records from the Current Contents® publications. SciSearch indexes all significant items (articles, review papers, meeting abstracts, letters, editorials, book reviews, correction notices, etc.) from approximately 4,500 major scientific and technical journals. Some 3,800 of these journals are further indexed by the references cited within each article, allowing for citation searching. An additional 700 journals indexed have been drawn from the ISI Current Contents® series of publications.

Manual, Alternative and Natural Therapy™ - MANTIS™

Manual, Alternative and Natural Therapy™ (MANTIS™) is a bibliographic database that provides coverage for health care disciplines not significantly represented in the major biomedical databases. International in coverage, the database contains references from more than 1,000 journals, with preference given to peer-reviewed journals. Approximately 70% of the references have abstracts. Searchable subject headings include Medical Subject Headings (MeSH®), plus a specialized supplemental controlled vocabulary in the areas of alternative medicine.

Allied and Complementary Medicine Database

The Allied and Complementary Medicine Database, formerly the Allied and Alternative Medicine Database, collects abstracts from over 400 biomedical journals as well as articles from other journals that deal with the topic of allied and alternative medicines. Established in 1985, this database is supported by the British Library Healthcare Information Service. After 1997, this database collected information concerning palliative care in addition to continuing to gather information about allied and alternative medicines.

CAB Health

The CAB International resource database, CAB Health, was established in 1973 and is updated quarterly. This database contains citations from both English and foreign language medical writings from over 130 countries. It has gathered over 500,000 citations relating to nutrition, protozoology, medical and veterinary entomology and mycology.

PsycINFO

The American Psychological Association's resource database PsycINFO contains citations and summaries of journal articles, book chapters, books, and technical reports, as well as citations to dissertations, in the field of psychology and psychological aspects of related disciplines, such as medicine, psychiatry, nursing, sociology, education, pharmacology, physiology, linguistics, anthropology, business, and law. Journal coverage, spanning 1987 to the present, includes international material selected from more than 1,300 periodicals written in over 25 languages. Current chapter and book coverage includes worldwide English-language material published from 1987 to the present. Over 55,000 references are added annually through regular updates.

Sociological Abstracts

Sociological Abstracts (SA) covers the world's literature in sociology and related disciplines in the social and behaviorial sciences. Over 1,600 journals and other serial publications are scanned each year to provide coverage of original research, reviews, discussions, monographic publications, panel discussions, and case studies. Conference papers and dissertations are also indexed in the file.

To ensure a comprehensive literature search, the EPC team also examined the reference lists from our database of reference material previously identified through the electronic searching, discussions with experts, and the article review process. In addition, the EPC team reviewed the list of journals that were cited most frequently in the literature searches and nominated additional journals likely to contain relevant articles (see Appendix B). The team reviewed the tables of contents of these journals for all issues published in 2001.

Search Terms and Strategies

The search strategies were designed to maximize sensitivity and were developed in consultation with team members. Preliminary strategies were developed to identify key articles. Using key articles determined to be eligible for review, the team developed and refined search

strategies in an iterative process. A strategy was first developed for PubMed. This strategy was then modified to create separate search strategies for each electronic database (see Appendix C).

Organization and Tracking of Literature Search

The results of both the MEDLINE® and DIALOG searches were downloaded from electronic sources, if possible, or manually entered into a ProCite database. The duplication check in the bibliographic software was used to eliminate articles already retrieved. This ProCite database was used to store citations and track search strategies and sources. The use of this software also allowed for the tracking of the abstract review process.

Abstract Review

As a first step in the review process, two members of the study team independently reviewed the titles identified by the search to exclude those that obviously did not meet our eligibility criteria:

1. written in English
2. includes human data
3. original data
4. information relevant to the management of hepatitis C
5. reports not only basic but also clinical sciences
6. applies to one of our key questions.

Excluded were:

7. meeting abstracts (no full article for review)
8. other incomplete reports (e.g., all data reported in a subsequent publication).

Differences between the two reviewers were adjudicated by other team members. Titles deemed not relevant by both reviewers were excluded from the abstract review process.

All remaining citations were included in the abstract review process. The EPC team developed an abstract review form (Appendix D) to screen the abstracts for relevance. This form was based on forms used in previous EPC reports. Each abstract was circulated to two members of the study team who independently reviewed the abstract and indicated which, if any, of the key questions the article addressed. For articles found not eligible, the reviewers indicated a reason for exclusion. When there was no abstract or when the reviewers could not determine from the abstract whether the article met the eligibility criteria, the team obtained a full copy of the article to review. Disagreements between members of the study team about eligibility were adjudicated at face-to-face meetings.

The EPC team applied the same eligibility criteria at the abstract review phase as listed above.

Qualitative and Quantitative Data Abstraction

The study team developed article review forms that were pilot tested and revised prior to use. The forms included a quality assessment form, a content abstraction form, and supplemental content abstraction forms for the biopsy and screening questions. On the quality assessment form, the reviewers indicated which of the key questions were addressed in the article.

To make sure that all articles met eligibility criteria, the study quality form began with a check of the eligibility criteria (see Abstract Review, above). In addition to the exclusion criteria listed on the abstract review form, the study quality form had other exclusion criteria that were used to focus the search on the studies that would be most valuable in addressing the key questions. These additional exclusion criteria included 1) all data reported in a subsequent publication; 2) some data related to a key question, but the study was not designed to address the question; 3) management of hepatitis C addressed in liver transplant patients only; 4) total number of study subjects less than 30 (as very small studies tend to be less rigorous and were not likely to provide enough valuable data to justify the extra effort needed to extract details from such studies); and 5) outcomes/results not measured according to an appropriate objective standard (i.e., virologic and/or histologic measures for questions 1b, 2a, 2c, and 2d; and histologic or pathologic evidence of HCC for questions 3a and 3b).

In our review of studies on key question 1b (relation of pre-treatment liver histology to outcomes of treatment), we included only randomized controlled trials because they would provide the strongest evidence on whether pre-treatment histologic findings are independent predictors of the efficacy of one treatment strategy compared to another. We were particularly interested in determining whether there is any evidence of an interaction effect between pre-treatment histology and the treatment regimens considered in key questions 2a and 2c. While cohort studies could provide some evidence of the relation between pre-treatment histology and the response to a given treatment regimen, they are susceptible to selection bias in that patients could be excluded from a cohort on the basis of pre-treatment histologic findings. This type of selection bias would make it difficult to determine whether the relative efficacy of different treatment regimens depends on histologic findings. For key question 1b, we also required at least 24 weeks of follow-up

For key question 1e, we included only studies that evaluated biochemical blood tests or serological tests that could serve as measures of liver fibrosis. These studies could include other tests, but we did not include studies that examined only other tests such as hematologic tests or radiologic imaging studies.

For key questions 2a and 2c, we included only randomized controlled trials that had a planned length of follow-up that was at least 24 weeks after the end of treatment. For key question 2d, we included only studies that had at least 5 years of follow-up, including studies of natural history without treatment.

For key question 3a, we looked for studies on patients with chronic hepatitis C that had at least 6 months of follow up for comparing one screening strategy to another or to no screening. For key question 3b, we included only studies that reported data on patients with hepatitis C although these studies could include some patients with only hepatitis B or patients co-infected

with HCV and HBV. We excluded studies that focused solely on hepatitis B because the pathophysiology and natural history of hepatitis C differs from that of hepatitis B.

As shown in Appendix E, the quality assessment form included 23 items about study quality in the following categories: representativeness of study population (five items); bias and confounding (four items); description of therapy/management (four items); outcomes and follow-up (five items); statistical quality and interpretation (four items); and conflict of interest (one item). The items in these categories were derived from study quality forms used in previous EPC projects and were modified to fit a focus on diagnostic and treatment issues in the management of chronic hepatitis C. Because of the divergence of issues covered by our key questions, not all items were required for each of the key questions.

The study team assigned each response level a score of zero (criteria not met), one (criteria partially met), or two (criteria fully met). The score for each category of study quality was the percentage of the total points available in each category for that study and therefore could range from zero to 100 percent. The overall quality score was the average of the first five categorical scores. For consistency with previous EPC reports, we did not include the conflict of interest item in the overall quality score because this was a new item that had not been included in the EPC's assessment of study quality in previous projects.

The content abstraction form included items that described the type of study, geographical location, the definition of study groups, the specific aims, the inclusion and exclusion criteria, screening test characteristics, demographic, social and clinical characteristics of subjects, and outcomes or results related to each of the key questions.

In our review of studies on key question 1b, we looked for the following types of data on: 1) univariate and multivariate analysis of pre-treatment histologic characteristics of patients that were associated with treatment response; and 2) treatment response rates in subgroups defined by pre-treatment liver histology. For studies that reported sustained virologic response rates or sustained histologic response rates in two or more treatment arms for two or more subgroups defined by specific histologic variables, we created a two by two or two by "n" table to record that information for each histologic variable. We used the data in these tables to perform multivariate logistic regression analyses that yielded odds ratios (with 95 percent confidence intervals) for the effect of treatment, effect of pre-treatment histology, and effect size of any potential interaction between treatment regimen and pre-treatment histology.

In our review of studies on key questions 2a and 2c (treatment of chronic hepatitis C), we also looked for data on 1) univariate and multivariate analysis of pre-treatment characteristics of patients that were associated with treatment response; and 2) treatment response rates in subgroups defined by HCV genotype. We focused on the latter because of the reported importance of HCV genotype in predicting response to treatment. For studies that reported sustained virologic response rates or sustained histologic response rates in two or more treatment arms for two or more subgroups defined by HCV genotype, we created a two by two or two by "n" table to record that information for the genotype variable. We used the data in these tables to perform multivariate logistic regression analyses that yielded odds ratios (with 95 percent confidence intervals) for the effect of treatment, effect of HCV genotype, and effect size of any potential interaction between treatment regimen and HCV genotype.

Article Review Process

The team reviewed each potentially eligible article identified by the abstract review process. At least one reviewer in each pair had clinical training, and at least one reviewer had training in epidemiology and research methods. One team member was responsible for completing both the quality assessment and content abstraction forms, and the second reviewed and confirmed the material abstracted. Differences between the two reviewers in either quality or content abstraction were resolved by consensus. Reviewers were not masked to author or journal names because previous work has shown that masking is unlikely to make a significant difference in the results of the data abstraction[15] and would have slowed the review process.

The team developed a Microsoft® Access 2000 (Copyright © 1992-9 Microsoft Corporation) database to collect, maintain, and analyze the quality assessment and content abstraction data. This database was also used to produce the evidence tables.

Evidence Tables

Evidence tables were constructed to present the information obtained on each key question. For each key question, the EPC team created a set of four tables, the first presenting basic information about study aims and eligibility criteria, the second presenting selected characteristics of study participants, the third presenting our assessments of study quality, and the fourth presenting selected results most pertinent to the key question.

Evidence Grades

Five members of the EPC team independently graded the strength of the evidence on each key question. If the team members disagreed about an evidence grade, the final grade given was based on the majority opinion. The grading scheme was derived from the scheme used in previous EPC projects.[16,17] For questions 2a, 2c, 2d, and 3a, the grades included the following:

Grade A (strong): Appropriate data available, including at least one well done randomized controlled trial; study population sufficiently large; adequate controls; data consistent; intervention clearly superior, equivalent or inferior to another strategy;

Grade B (moderate): Appropriate data available; study population sufficiently large; adequate controls; data reasonably consistent; intervention data indicate superiority or equivalence of one intervention compared to another; intervention likely to be superior, equivalent, or inferior to another but insufficient evidence to conclude definitively;

Grade C (weak): Some data available; study population reasonably large; data indicate trend supporting benefit (or equivalence) of one intervention compared to another; insufficient evidence to conclude that intervention is likely to be superior, equivalent or inferior to another;

Grade I (insufficient): Appropriate data not available or insufficient number of patients studied.

For questions 1b, 1e and 3b, the grades were as follows:

Grade A (strong): Appropriate data available, including at least one well done study; study population sufficiently large; adequate reference standard; data consistent; test definitively is or is not useful;

Grade B (moderate): Appropriate data available; study population sufficiently large; adequate reference standard; data reasonably consistent; data indicate test is or is not likely to be useful but insufficient evidence to conclude definitively;

Grade C (weak): Some data available; study population reasonably large; insufficient evidence to conclude that test is or is not likely to be useful;

Grade I (insufficient): Appropriate data not available or insufficient number of patients studied.

Peer Review Process

A copy of the draft report was sent to the core technical experts and the peer reviewers, as listed in Appendix A. Each expert/reviewer was asked to comment on the form and content of specific sections of the report, according to their areas of expertise and interest, and was invited to comment on all other parts as well. The EPC team incorporated the reviewers' comments into the final report.

Chapter 3: Results

Literature Search and Abstract Review

The literature search process identified 3,349 unique potentially relevant citations. The first complete set of searches was completed in September 2001, with updated searches carried out in March of 2002.

Through the review of titles of the identified citations, 1,745 citations were determined eligible for abstract review. Of these, 24 had been included in previous systematic reviews, and were dropped from further review. Of the remaining 1,721 citations, 72 percent (1,237 articles) did not meet the criteria for article review. Abstracts were excluded for the following reasons: the article was not in English (1); the article did not include human data (8); the article did not present any original data (180); the article did not contain information relevant to the management of hepatitis C (54); the article reported only on basic science (66); the article did not address one of the EPC's key questions (555); the article related only to key question 2a or key question 2c, and was not a randomized controlled trial (389); the article addressed only key question 2a, and reported on treatment with interferon alone, without an analysis of any patient subgroups of interest (5); the article addressed only key question 2d, and did not have at least 60 months of followup (6); the study did not use appropriate objective outcomes (1); the total study population of the article was less than 30 patients (59); the article did not include at least 24 weeks of follow-up (2); the article was a case report (14); the article presented only editorial material (6); the article was a cost-effectiveness analysis (1); the article reported on therapies that were not treatment options of interest (5); the article addressed only key question 1e, but the test used was not biochemical or serologic (15); the article dealt only with patients after liver transplant (1); the article answered only key question 1b and did not meet the team's methodology requirements (3); or no copy of the article could be obtained (1). The total number of reasons for exclusion exceeded the number of abstracts reviewed because the paired reviewers did not have to agree on the reason for the exclusion, only that the citation was excluded.

Article Review

Following the abstract process, 486 articles remained eligible for review. Of these, 150 articles were tagged for key question 1b (relation of initial biopsy results to treatment outcomes) or key question 1c (relation of follow-up biopsy results to outcomes of treatment), 108 pertained to key question 1e (use of tests to predict biopsy findings), 163 addressed key questions 2a or 2c (current treatment options), 73 addressed key question 2d (long-term outcomes of current treatment options), and 52 addressed either key question 3a or key question 3b (screening for HCC). The total number of articles pertaining to key questions exceeded the number of articles reviewed because some articles were identified as relevant for more than one key question.

At article review, 129 articles were excluded from the 150 articles originally identified for possible relevance to key question 1b. Of these, 15 were not relevant to any of the EPC team's key questions, two were related to HIV rather than HCV, one included fewer than 30 HCV

patients, one did not use suitably objective outcomes, seven had a total study population of less than 30 patients, and four did not have at least 24 weeks of follow-up. Thirty-two articles did not apply to key question 1b, and were recorded as being excluded for reasons relevant to other key questions. Seventy-eight articles did not meet the EPC team's previously described methodology requirements for articles relevant to key question 1b. Following article review, 21 articles remained eligible for the review on key question 1b.

At article review, 42 articles were excluded from the 108 articles originally identified for possible relevance to key question 1e. Of these, 8 were not relevant to any of the EPC team's key questions, 11 were not designed specifically to answer one of the team's key questions, four contained no data that could be extracted systematically. Seven reported on tests were were not biochemical nor serological, not intended to measure fibrosis, or not regularly available to clinicians. Five articles had a total study population of fewer than 30 patients, and five studies were not relevant to key question 1e and were excluded for reasons relevant to other key questions. Following article review, 66 articles pertaining to key question 1e remained.

At article review, 117 articles were excluded from the 163 articles originally identified for possible relevance to key question 2a or 2c. Of these, one did not apply to any key question, 31 did not report on therapies of interest, one study's data was all reported in a subsequent publication, two were not randomized controlled trials, 64 reported on interferon monotherapy and did not include subgroups of interest , four did not use suitably objective outcomes, nine articles had a total study population of less than 30 patients, and five articles were not relevant to key question 2a or key question 2c and were excluded for reasons pertaining to other key questions. Of the remaining 46 articles, 16 pertained to key question 2a, and 30 pertained to key question 2c.

At article review, 33 articles were excluded from the 73 initially identified for possible relevance to key question 2d. Of these, one was not in English, two contained no original data, five did not pertain to any of the EPC team's key questions, one had no data that could be extracted, one study had fewer than 30 HCV patients, 16 did not have at least 60 months of follow-up, one did not have suitable objective outcomes, one article had a total study population of less than 30 patients, and five articles were not relevant to key question 2d and were excluded for reasons pertaining to other key questions. Following article review, 40 articles remained relevant to key question 2d.

At article review, 28 articles were excluded from the 52 initially identified for possible relevance to key question 3a or 3b. Of these, ten were not relevant to any key question, four contained no data that was extractable, five reported on screening tests that are not routinely available to clinicians, two articles had a total study population of less than 30 patients, one study had fewer than 30 HCV patients, one did not use suitably objective outcomes, one study did not have at least 24 weeks of follow-up and two studies were not relevant to questions 3a or 3b and were excluded for reasons pertaining to other key questions. Following article review, one study was identified as relevant to key question 3a, and 23 studies were relevant to key question 3b.

Q1b *How well do the results of initial liver biopsy predict outcomes of treatment in patients with chronic hepatitis C, taking into consideration patient characteristics such as viral genotype?*

Results of Literature Search

As indicated above, we identified 21 studies that were eligible for our review on key question 1b. Of these 21 studies, 14 were also included in our review of studies on key questions 2a and 2c, and seven were studies of interferon-based therapies not included in key question 2a or 2c. We did not include studies that were included in the previous systematic reviews that we reviewed for questions 2a and 2c.

Characteristics of Studies on the Relation of Initial Liver Biopsy Results to Outcomes of Treatment

Evidence Table 1 summarizes the specific aims and patient eligibility criteria of the 21 studies that met our criteria for key question 1b. Most studies were conducted in the United States or Europe, but one study was in Asia and a few studies recruited patients from Australia. Almost all studies were at least co-sponsored by the pharmaceutical industry. Almost all studies excluded patients with other forms of liver disease, including hepatitis B, and several excluded patients with decompensated liver disease. Most also excluded women who were pregnant or breast feeding, patients with active intravenous drug use, heavy alcohol use, anemia, HIV infection, or other significant co-morbidity.

Evidence Table 2 summarizes the demographic and clinical characteristics of the study populations. In all of the studies, the majority of participants were men with the mean age ranging between 34 and 59 years. The mean serum alanine aminotransferase (ALT) was between 65 and 200 mg/dl with the duration of infection ranging from 5.5 to nearly 20 years. The distribution of the initial liver biopsy findings was varied with many studies using different reporting methods; however, there were both cirrhotics and noncirrhotics included in all treatment groups. Genotypes were obtained routinely and varied according to the country in which the study was performed.

Quality of Studies on the Relation of Initial Liver Biopsy Results to Outcomes of Treatment

All studies pertaining to this question were randomized controlled trials. As shown in Evidence Table 3, the median overall quality score for the studies was 64 percent with a range of 31 to 75 percent. The 25 percent and 75 percent interquartile ranges were 56 percent and 70 percent. Most of the studies had a representativeness score, outcomes score and statistical analysis score greater than or equal to 75 percent. Although these studies generally used appropriate methods for measuring outcomes, very few reported on the incidence of complications from the liver biopsy. Also, the bias and description scores tended to be lower than the scores in the other categories. For question 1b, the assessment of potential bias and

confounding was based on a question about whether the study performed an independent and blind comparison of the outcomes to the biopsy results. Only a minority of studies met this criterion fully. Some studies reported that the outcome assessment was independent of the biopsy readings but did not indicate whether it was blinded (yielding a score of 50 percent). Other studies did not report either element explicitly (yielding a score of 0 percent). The description score for question 1b was based on the adequacy of the study's description of the technique and size of the liver biopsy. Surprisingly few studies provided this important information. Finally, only a few studies identified both the source of funding and the type and degree of involvement of the funding agency.

Results of Studies on the Relation of Initial Liver Biopsy Results to Outcomes of Treatment

Results were presented in several ways (see Evidence Table 4). Twelve studies presented multivariate analysis with pretreatment histologic results considered as an independent variable in predicting virologic or histologic outcomes. Eight studies presented univariate analyses of baseline histologic results and their association with outcomes, and three studies presented data on pretreatment histologic results stratified by treatment group or virologic or histologic outcome. Only six studies reported enough data to permit us to perform a multivariate logistic regression analysis of the effects of pre-treatment histological abnormalities on the efficacy of treatment options.

Multivariate analysis Among the studies that used multivariate analysis, one compared pegylated (peg) interferon and ribavirin with standard interferon alpha-2b and ribavirin,[18] four evaluated standard interferon in combination with ribavirin versus standard interferon alone,[19-21] one evaluated peginterferon versus standard interferon alpha-2b,[13] one evaluated peginterferon versus standard interferon alpha-2a,[22] three evaluated different doses of interferon alone, or different types of interferon treatment,[23,24] one study evaluated standard interferon and amantadine versus standard interferon alone,[25] and one study evaluated standard interferon with colchicine.[26] In the study with peginterferon and ribavirin, the absence of cirrhosis was associated with sustained virologic response to therapy in both univariate and multivariate analyses.[18] In one of the studies with ribavirin and standard interferon, the multivariate analysis did not show a significant association between sustained viral response and initial histologic grade, initial histologic stage, or initial presence or absence of cirrhosis.[19] In another study with ribavirin and standard interferon alpha-2b, the multivariate analysis showed a significant association between pretreatment fibrosis and virologic nonresponse to treatment, but the p values and parameter estimates were not provided in the text of the article.[20] The third study with standard interferon and ribavirin found no significant association between pretreatment grade and ultimate response to therapy in multivariate analysis.[21] This study did demonstrate a significant association between pretreatment fibrosis and virologic response in univariate analysis. In the study evaluating peginterferon versus standard interferon alpha-2b, baseline histologic results were not associated with sustained virologic response, although the histologic response rates were higher than the virologic response rates.[13] In contrast, in the study with peginterferon compared to interferon alpha-2a, there was a significant association between virologic response and the absence of cirrhosis or fibrosis.[22]

In one study evaluating different doses of interferon, the pretreatment Knodell index was a significant predictor of treatment response.[23] In another study, the histologic activity index (HAI) was not a predictor of response.[24]

Finally, in the study evaluating standard interferon and amantadine, there was no significant association between pretreatment histologic findings and virologic response to therapy.[25] In the study of standard interferon and colchicine, however, lower stage on pretreatment biopsy did predict a virologic response to treatment in both univariate and multivariate analysis. Interestingly, in this study lower grade did not predict virologic response to treatment.[26]

Univariate analysis Multiple studies performed univariate analyses to assess the association between initial liver biopsy results and virologic or histologic outcomes. Five studies evaluated standard interferon alone in univariate analysis,[27-31] two evaluated standard interferon with ribavirin,[32,33] and one study evaluated standard interferon with amantadine versus standard interferon alone.[34]

The results of the studies with standard interferon alone were mixed, with two studies demonstrating a significant association between baseline histology and response to treatment,[28,29] two studies demonstrating no association between pretreatment biopsy findings and response to treatment,[27,31] and one study demonstrating a significant association of pretreatment biopsy findings with biochemical response but not with virologic or histologic outcomes.[30]
In the study with standard interferon and amantadine[34] and the studies of interferon and ribavirin, [32,33] pretreatment biopsy findings did not predict virologic response to treatment.

Analysis stratified by outcome When the analysis of the relation between biopsy results and outcome was stratified by outcome, results were mixed. Some studies performed univariate analysis of pretreatment stage by treatment group. One study that stratified by outcome evaluated three different types of interferon (recombinant, leukocyte, and fibroblast).[35] In this study, sustained responders had lower baseline HAI scores than did nonresponders, both within each treatment group and compared to other groups, but the actual HAI scores were presented only as graphical data.[35]

Analysis stratified by treatment In two studies, results were stratified by treatment group. One study examined standard interferon with and without ribavirin,[36] and the other compared standard interferon with peginterferon.[37] In the interferon and ribavirin study, pretreatment histologic results did not predict response in the group treated with standard interferon and ribavirin, but fibrosis stage did predict response in the interferon-alone group.[36] In the study comparing standard interferon with peginterferon the virologic response was similar in those patients with bridging fibrosis and those with cirrhosis. In addition, HAI scores were not predictive of virologic response.[37]

Other Data on Relation of Biopsy Results to Outcomes of Treatment

Six studies reported enough data to permit a multi-variate logistic regression analysis of the relation of pre-treatment liver histology to the effect of the treatment regimens on the SVR rate (see Table 1 at end of chapter). The resulting analyses indicated that pre-treatment histology was not consistently associated with an independent effect on SVR rate and the studies were

relatively consistent in finding no interaction between pre-treatment histology and the effect of different treatment regimens.

Summary of the Relation of Initial Liver Biopsy Results to Outcomes of Treatment

The published evidence on the relation of pretreatment liver biopsy findings to outcomes of treatment is extremely heterogeneous and has important methodologic limitations. Specific limitations are lack of reporting of parameter estimates and confidence intervals from univariate and multivariate analysis as well as limited evaluation of interaction effects between baseline histology and treatment. Recognizing these limitations and using the studies with the strongest type of analysis for this key question (i.e., multivariate analysis), we found that these studies were relatively, but not entirely, consistent in suggesting that the presence of advanced fibrosis or cirrhosis may predict a modest decrease in the likelihood of having a sustained virologic response to treatment [Evidence Grade B].

Q1e *How well do biochemical blood tests and serological measures of fibrosis predict the findings of liver biopsy in patients with chronic hepatitis C?*

Results of Literature Search

As indicated in the previous section, we found 66 studies that met all of our eligibility criteria for this key question.

Characteristics of Studies on Tests for Predicting Biopsy Findings

Evidence Table 5 summarizes the specific aims, patient eligibility criteria, geographic location, and funding source of the studies that met our criteria for key question 1e. The main inclusion criterion was evidence of chronic hepatitis C. A common method for documenting HCV was the presence of viral RNA in serum. Several studies reported the distribution of patients by HCV genotype with the percentage of patients with genotype 1b ranging from 26 to 92 percent.

The most common exclusion criteria were evidence of hepatitis B infection (24 studies), heavy alcohol use (21 studies), presence of other liver diseases (18 studies), previous antiviral treatment (17 studies), immune system disorders (16 studies), and HIV infection (12 studies).

Evidence Table 6 shows selected demographic and clinical characteristics of the study groups in each study. Most of the studies used a cross-sectional or diagnostic test design, but a few studies used a prospective cohort design. In a few studies, a first set of patients was used to develop a statistical model predicting fibrosis, and the results were validated in an independent second set of patients.[38-40] The mean age of the study populations ranged from 17 to 65 years. The percentage of subjects that were male ranged from 30 to 58 percent with a median of 48 percent. The mean fibrosis score by the HAI ranged from 34 percent to 94 percent. Histological

evidence of liver fibrosis was evaluated with several different staging systems including the MHAI stage, HAI, METAVIR, Scheur, Desmet, and other systems.

Quality of Studies

The median overall quality score for the studies on question 1e was 62 percent with a range from 11 to 88 percent (see Evidence Table 7). Most of the studies had scores greater than or equal to 75 percent for the study quality categories of representativeness, bias and confounding, and statistical analysis. The scores for description of the liver biopsy methods were low because very few studies reported details on the type of needle biopsy and size of the liver core. Few studies had scores greater than or equal to 75 percent for the category of outcome assessment, and none of the studies reported on side effects or adverse outcomes after liver biopsy.

Results of Studies on Tests for Predicting Biopsy Findings

Nineteen studies investigated a single serum test as a measure of liver fibrosis and the remainder used two or more markers. The results of these studies are summarized in Evidence Table 8.

Serum ALT and AST. Serum ALT was the most commonly investigated marker.[40-54] It was statistically associated with fibrosis stage in 11 of 15 studies,[40,45-54] with sensitivity ranging from 61 to 76 percent,[50,52] and specificity ranging from 44 to 66 percent.[50,52] Serum ALT as a single marker of fibrosis showed areas under the curve of 0.75 or less by receiver operating characteristic (ROC) analysis.[40,52,53] Multivariate models of predictors of fibrosis did incorporate serum ALT in two studies.[40,45] In contrast, the ratio of aspartate aminotransferase (AST) to ALT was a specific but insensitive predictor of cirrhosis, with a sensitivity ranging from 31 to 56 percent and specificity of 90 percent to 100 percent.[55-58] One study calculated a negative predictive value of 88 percent and a positive predictive value of 74 percent for use of the AST/ALT ratio in predicting fibrosis.[57] Little information was reported on the role of AST/ALT ratio in predicting noncirrhotic stages of fibrosis.

Extracellular matrix tests Twenty-six studies investigated components of the extracellular matrix and/or markers of extracellular matrix degradation (Evidence Table 8). Markers of extracellular matrix included hyaluronic acid (HA), procollagen type III peptides (P-III-P), type IV collagen, 7s collagen, laminin, and fibronectin. Markers of matrix degradation included MMP-2, MMP-7, MMP-9, and TIMP-1-4. Though these markers showed broad overlap for any given fibrosis stage, they were still significantly associated with fibrosis in every study examined, except for one study in which P-III-P was not associated with fibrosis.[59] Hyaluronic acid correlated best with fibrosis stage overall, with correlation coefficients ranging from 0.42 to 0.79. Hyaluronic acid had sensitivities ranging from 47 to 88 percent and specificities ranging from 59 to 100 percent, and laminin had sensitivities of 52 to 80 percent with specificities of 80 to 85 percent. P-III-P correlation coefficients ranged from 0.30 to 0.51 and from 0.26 to 0.43 for type III collagen. P-III-P had a sensitivity ranging from 34 to 89 percent and specificity of 21 to 86 percent. Markers of extracellular matrix degradation such as TIMP were also associated significantly with fibrosis as single markers, but were generally less predictive than hyaluronic acid.

Other tests A number of cytokines and cytokine receptors were also investigated including tumor necrosis factors TNF-R55, TNF-R75, and TNF alpha,[60] as well as serum interleukin (IL)-2 receptors.[61] Except for TNF-alpha, the cytokine and cytokine receptors were significantly associated with fibrosis, but were less predictive than markers of extracellular matrix. In contrast, TNF-alpha was significantly associated with hepatic inflammation but not with fibrosis.

As shown in Evidence Table 8, a variety of other tests were investigated including glutathione,[46] alpha-fetoprotein,[42,62,63] prothrombin time,[38,39,51] PCHE,[38] Mn-SOD,[38] beta-NAG,[38] alpha-2-macroglobin,[38] beta-globulin,[38] albumin,[38,51] gamma glutamyl transpeptidase,[38,39,51] bilirubin,[39,40,51] LDH,[51] serum AST,[39,51] alkaline phosphatase,[51] white blood cell count,[51] creatinine,[39] total bile acids,[64] GGT,[64] and immunoglobulin G.[65] Similar to the cytokines, these tests frequently were statistically associated with fibrosis. However, these markers appeared less useful as a group than did the markers discussed above, and only limited data were available on these markers. The platelet count, an indicator of portal hypertension, was also a predictor of cirrhosis in three studies, both in isolation and in studies employing panels of markers.

Test panels Five of the studies,[38-40,50,51] used large panels of markers (greater than or equal to 5 markers) and achieved the greatest predictive values, with sensitivities ranging from 50 to 82 and specificities of 35 to 80 percent. Of these studies, a panel of MMP-2, IV-C7S, and hyaluronic acid optimally predicted no fibrosis/minimal fibrosis, with a sensitivity of 68.3 percent and specificity of 73 percent. However, up to 94 percent of cirrhotic patients could be correctly identified using multivariate models.[38] In another multivariate model using different markers, moderate to severe inflammation and/or bridging fibrosis to cirrhosis could be identified with a specificity of 95 percent and sensitivity of 52 percent.[39]

General observations All of the above studies used statistical tests to show correlations/associations between serum tests and histological evidence of liver fibrosis. Additionally, some studies reported the levels of their serological marker by fibrosis stage. They uniformly reported broad overlap between each fibrosis stage, with a general trend toward increased levels of the serological marker with increasing levels of fibrosis. Because of the broad overlap for any given histological stage of fibrosis, the tests were best at predicting the absence of fibrosis (or minimal fibrosis) or identifying those with advanced fibrosis/cirrhosis. Serologic tests were less effective in classifying intermediate stages of fibrosis.

Summary of Tests for Predicting Biopsy Findings

The published evidence was very heterogeneous regarding the utility of biochemical tests and serologic measures of fibrosis in predicting fibrosis in liver biopsy in chronic hepatitis C. The studies assessed numerous tests using a variety of methods for reporting results. Most of the studies had important limitations in one or more categories of study quality. Nonetheless, the studies were relatively consistent in showing that 1) serum liver enzymes have only modest value in predicting fibrosis on liver biopsy [Evidence Grade B], 2) the extracellular matrix tests, hyaluronic acid and laminin, may have value in predicting fibrosis on liver biopsy [Evidence Grade B], 3) cytokines have less value than the extracellular matrix tests in predicting fibrosis on liver biopsy [Evidence Grade B], and 4) panels of tests including MMP-2, IV-C7S, and hyaluronic acid may have the greatest value in predicting the absence of more than minimal

fibrosis on liver biopsy and in predicting the presence of cirrhosis on biopsy [Evidence Grade B]. None can consistently classify intermediate stages of fibrosis.

Q2a *What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients, including peginterferon plus ribavirin, peginterferon alone, interferon plus ribavirin, and interferon plus amantadine?*

Results of Literature Search

We found 46 studies that met our eligibility criteria for key questions 2a or 2c, including studies that examined the efficacy and/or safety of treatment of chronic hepatitis C in the following patient populations:

1. treatment-naive patients (peginterferon alpha plus ribavirin in three studies; peginterferon alpha monotherapy in four studies; interferon alpha plus ribavirin in four studies; and interferon alpha plus amantadine in five studies);
2. patients who had not responded to previous interferon treatment (23 studies);
3. patients who had relapsed after previous interferon treatment (14 studies); and
4. clinically important subgroups of HCV-infected patients including patients with hemophilia (one study) or chronic renal insufficiency (one study), hepatitis B (one study), and subgroups defined by race/ethnicity (two studies).

In addition, data from previously published meta-analyses and/or systematic reviews met criteria for key questions 2a or 2c, including treatment-naive, relapsing and nonresponding patient populations.[66-68]

Studies on Peginterferon Alpha Plus Ribavirin for Chronic Hepatitis C in Treatment-naive Patients

Characteristics of the studies Three randomized controlled trials examined therapy with peginterferon and oral ribavirin.[12,18,69] Unfortunately, the results of the study by Fried et al,[69] have not yet been published, although the results have been presented at professional meetings.

Evidence Table 9 describes the aims of these trials and their eligibility criteria. The studies required a serum alanine aminotransferase greater than the upper limit of the normal range, quantifiable serum HCV RNA, and normal hematologic parameters. In addition, patients were excluded if they had HIV infection, previous interferon therapy, decompensated liver disease, other causes of liver disease, or significant medical or psychiatric co-morbidity.

These studies aimed to assess the safety and efficacy of peginterferon and ribavarin combination therapy. As shown in Evidence Table 10, Manns[18] compared peginterferon alpha-2b 1.5 µg/kg per week plus ribavirin 800 mg per day for 48 weeks to peginterferon 1.5 µg/kg for four weeks followed by 0.5 µg/kg for 44 weeks with ribavirin 1000-1200 mg per day for 48 weeks, and to standard interferon alpha-2b 3 million units (MU) three times per week plus ribavirin 1000-1200 mg per day for 48 weeks. In a dose finding study, Glue [12] compared six different treatment regimens for 24 weeks, three with three different doses of peginterferon plus

ribavirin, and three with varying doses of peginterferon alone. Although the results of the study by Fried et al[69] have not been published yet and thus are not included in the evidence tables, a published abstract reported that this study compared 180 µg of peginterferon alpha-2a once per week in combination with ribavirin 1000-1200 mg per day to standard interferon alpha-2b 3 million units (MU) three times per week plus ribavirin 1000-1200 mg to180 µg of peginterferon alpha-2a alone. The total treatment duration was 48 weeks.

Evidence Table 10 also summarizes the demographic and clinical characteristics of the patients enrolled in these studies. The study by Manns[18] was large. The mean age was 42 years; the percentage of males was 62 percent; and 64 percent had HCV genotype 1. Glue's study population was smaller (only 72 patients), had a lower mean age of 39.8 years, and a lower percentage of patients with genotype 1 (45 percent) than the other study.[12]

Quality of studies Evidence Table 11 summarizes the quality of these studies. The overall quality scores for the studies were 85 percent and 56 percent. The study by Manns et al, had a quality score greater than or equal to 75 percent for the five main study quality categories. The small study by Glue et al had a quality score greater than or equal to 75 percent for only two of the study quality categories. Neither study reported the type or degree of involvement of the funding source.

Results of studies Evidence Table 12 summarizes the results of these studies. Manns and colleagues treated the patients for 48 weeks and followed them for an additional 24 weeks.[18] The investigators did not report any statistically significant difference in biochemical ETR or sustained response among the three groups. However, 65 percent of patients in the high dose peginterferon
(1.5 µg/kg for 48 weeks) plus ribavirin group had a virological ETR compared with 54 percent in the standard interferon plus ribavirin group ($p<.001$) and 56 percent in the low dose peginterferon (1.5 µg/kg for 4 weeks then 0.5 µg/kg) plus ribavirin group. Moreover, 54 percent of the high dose peginterferon plus ribavirin group had a sustained virological response compared with 47 percent in the other two treatment groups ($p < 0.01$). Also, patients with genotype 1 had a significantly greater virological response to the high dose peginterferon plus ribavirin therapy compared with standard interferon plus ribavirin treatment ($p < 0.05$). Paired biopsies were performed in 68 percent of patients. All three treatment groups demonstrated improvement in histological evidence of inflammation and fibrosis, but there was no significant difference between the groups. Predictors of virological response included non-1 genotype, low baseline viral load, dose of peginterferon plus ribavirin treatment, younger age, and lack of bridging fibrosis. Dose discontinuation for adverse events occurred in 14 percent of patients in the high dose peginterferon plus ribavirin group versus 13 percent in the other two groups.

Glue compared six different treatment regimens in groups treated for 24 weeks and followed them for an average of 24 weeks (see Evidence Table 12). The investigators found that patients receiving 1.4 µg/kg of peginterferon 2b plus ribavirin had a 60 percent SVR rate compared to 53 percent in patients given 0.7 µg/kg of peginterferon plus ribavirin and 17 percent in patients receiving 0.35 µg/kg of peginterferon. Statistical significance was not reported. Five patients discontinued therapy: one secondary to neutopenia, two due to alcohol abuse, and two for personal reasons.

Summary Evidence on the efficacy of peginterferon and ribavirin, based on one large and one small dose finding study, is limited by our lack of access to the results of an additional large randomized trial. The two available studies are consistent in demonstrating the efficacy of peginterferon plus ribavirin in treatment-naive patients with chronic hepatitis C [Evidence Grade A].

Studies on Peginterferon Alone for Chronic Hepatitis C in Treatment-naive Patients

Characteristics of the studies Four studies assessed the safety and efficacy of peginterferon alone in treatment-naive patients with chronic hepatitis C.[13,22,37,70] See Evidence Table 9 for the study aims and eligibility criteria. Three of these studies examined the safety and efficacy of peginterferon-alpha-2a, and one study examined peginterferon-alpha-2b.[13] All four of these studies required an initial liver biopsy and an elevated ALT. All studies with the exception of Heathcote et al[37] required detectable HCV in the serum. In addition, all studies excluded patients previously treated with interferon as well as patients who had HIV infection, other causes of liver disease (including hepatitis B), abnormal hematologic parameters, and major medical and psychiatric co-morbidity. Furthermore, two studies excluded active intravenous drug users.[13,70] Finally, one study by Heathcote and colleagues included only patients with histologic evidence of advanced hepatic fibrosis (e.g., cirrhosis or bridging fibrosis) on biopsy.[37]

Evidence Table 10 describes the study groups and the baseline characteristics of the patients in these four randomized controlled trials. Zeuzem[22] compared patients receiving peginterferon alpha-2a 180 µg weekly for 48 weeks to standard interferon alpha-2a 6 MU three times per week for 12 weeks followed by 3 MU three times per week for 36 weeks in persons naive to HCV treatment. Reddy and colleagues[70] randomized patients to standard interferon alpha-2a, peginterferon alpha-2a 45 µg weekly, peginterferon alpha-2a 90 µg weekly, peginterferon alpha-2a 180 µg weekly, or peginterferon alpha-2a 240 µg weekly administered for 48 weeks in HCV treatment-naive subjects. The third study, by Heathcote[37] was an open-label randomized controlled trial of the safety and efficacy of standard interferon 3 MU three times per week for 48 weeks compared to peginterferon alpha-2a 90 µg and 180 µg weekly for 48 weeks in HCV treatment-naive patients with histological evidence of cirrhosis or fibrosis. Finally, Lindsay et al.[13] performed a randomized controlled trial evaluating the efficacy of standard interferon alpha-2b 3 MU three times per week for 48 weeks to three doses of peginterferon alpha-2b 0.5 µg per kilogram, 1.0 µg/kg and 1.5 µg/kg for 48 weeks in HCV-infected persons naive to HCV treatment.

The demographic characteristics were heterogeneous across studies. The mean age for the study performed by Zeuzem et al.[22] was 41 years old; 67 percent of the study group was male and 86 percent was white, 10 percent was black, and 10 percent was Asian; 61 to 63 percent had genotype 1. Only 4 percent in the peginterferon group and 10 percent in the standard interferon group were cirrhotic. There was no significant difference among the treatment groups. The mean age in Reddy's study[70] ranged from 41.6 to 43.1 years among the treatment groups. The percent of whites ranged from 78.7 percent in the standard interferon group to 90 percent in the peginterferon 45 µg group. The percentage of blacks ranged from 0 percent in the peginterferon 90 µg group to 12.5 percent in the standard interferon therapy group. The percent with genotype

1 ranged from 63 percent in the peginterferon 270 µg group to 81.8 percent in the standard interferon alone group. Heathcote and colleagues [37] had three treatment groups with an average age ranging from to 46.9 to 47.2 years. The percentage of males ranged from 70 to 74 percent and the percentage that were white ranged from 86 to 91 percent. Fifty to 55 percent of the patients had genotype 1. Twenty to 24 percent of the patients had bridging fibrosis and the remainder had cirrhosis. There were no significant differences across the treatment groups. The mean age in the study performed by Lindsay et al.[13] ranged between 42.6 and 43.7 years, 49.5 to 68.3 percent were male, and 74.4 to 90.9 percent were white. The proportion of patients who had genotype 1 ranged between 58 and 71.6 percent.

Quality of studies Evidence Table 11 summarizes the quality of these studies. The total quality score ranged from 68 to 91 percent with a median score of 77 percent. All four studies had a quality score of at least 50 percent in all five of the main study quality categories. Only one of the four studies reported the type or level of involvement of the funding source.

Results of the studies Evidence Table 12 summarizes the results for these studies. Zeuzem and colleagues [22] treated their patients for 48 weeks and followed them for an additional 24 weeks. They found that virological ETR and SVR was observed in a greater number of subjects receiving peginterferon alpha-2a 180 µg (ETR 69 percent and SVR 39 percent) than in those receiving standard interferon alpha-2a (ETR 28 percent and SVR 19 percent; $p < 0.01$ for both). Of those subjects with paired liver biopsies, histological improvement (defined as at least a 2-point improvement in HAI score from baseline) was observed as follows: standard interferon alpha-2a (92 subjects); and peginterferon alpha-2a 180 µg (116 subjects). Histological response was found in 44 percent and 47 percent of patients who failed to achieve an SVR. Seven percent of patients in the peginterferon group discontinued treatment compared to 10 percent of patients in the interferon-alone group.

Reddy et al,[70] comparing standard interferon to four different dosing regimens of peginterferon alpha-2a, observed a greater virological ETR and sustained response in subjects receiving peginterferon alpha-2a 180 µg (ETR 60 percent and SVR 36 percent) and peginterferon alpha-2a 240 µg (ETR 56 percent and SVR 29 percent) than in those receiving standard interferon alpha-2a (ETR 12 percent and SVR 3 percent), peginterferon alpha-2a 45 µg (ETR 30 percent and SVR 10 percent), or peginterferon alpha-2a 90 µg (ETR 45 percent and SVR 30 percent). For SVR, the *p* values observed compared with standard interferon alpha-2a were as follows: peginterferon alpha-2a 45 µg (> 0 .05), 90 µg (< 0.01), 180 µg (< 0.001), and 240 µg (< 0.01). Of those subjects with paired liver biopsies, histological improvement (defined as at least a 2-point improvement in HAI score from baseline) was observed as follows: standard interferon alpha-2a (57 percent); peginterferon alpha-2a 45 µg (47 percent), 90 µg (59 percent), 180 µg (63 percent) and 240 µg (66 percent) ($p > 0.05$ for all comparisons). There were more withdrawals secondary to adverse events in the peginterferon groups than in the standard interferon group (10 percent, 0 percent, 22 percent, 20 percent, and 9 percent, respectively).

Heathcote and colleagues,[37] studying patients with cirrhosis or bridging fibrosis, observed that the virological ETR rate and SVR rate for the peginterferon alpha-2a 180 µg group (ETR 44 percent and SVR 30 percent) were significantly greater compared to standard interferon therapy alpha-2a (ETR 14 percent and SVR 8 percent; $p < 0.001$). Patients who received peginterferon alpha-2a 90 µg were also found to have a significantly greater ETR rate, but this difference was

not sustained (ETR 42 percent and SVR 15 percent). Among the subset with paired liver biopsies, histological improvement (defined as at least a 2-point improvement in HAI score) was observed as follows: standard interferon alpha-2a (31 percent), peginterferon alpha-2a 90 µg (44 percent), and peginterferon alpha-2a 180 µg (54 percent) ($p = 0.02$ for comparison of peginterferon 180 µg and standard interferon alpha). Treatment discontinuation secondary to adverse events occurred in 14 percent of patients receiving standard interferon, 2 percent of patients in the 90 µg peginterferon group, and 13 percent of patients receiving 180 µg of peginterferon.

Lindsay and colleagues[13] studied the efficacy and safety of peginterferon alpha-2b in treatment-naive patients. They found that all of the peginterferon groups had significantly greater virological ETR and SVR rates compared to those receiving standard interferon therapy. The percentage of patients with virological ETR and SVR were as follows: peginterferon alpha-2b 1.5 µg (ETR 49 percent and SVR 23 percent), peginterferon alpha-2b 1.0 µg (ETR 41 percent and SVR 25 percent), peginterferon alpha-2b 0.5 µg (ETR 33 percent and SVR 18 percent), and standard interferon alpha-2a (ETR 24 percent and SVR 12 percent). Among the subset with paired liver biopsies, histological improvement (defined as at least a 2-point improvement in HAI score) was observed as follows: standard interferon alpha-2b (47 percent), peginterferon alpha-2b 0.5 µg (49 percent), peginterferon alpha-2b 1.0 µg (50 percent), and peginterferon alpha-2b 1.5 µg (48 percent). Treatment was discontinued because of adverse effects as follows: standard interferon alpha-2b (9 percent), peginterferon alpha-2b 0.5 µg (9 percent), peginterferon alpha-2b 1.0 µg (11 percent), and peginterferon alpha-2b 1.5 µg (9 percent).

Summary Evidence on the efficacy of peginterferon alone was heterogeneous and had important methodologic limitations. Among the studies, the racial and genotypic composition varied. In addition, there were differences in the proportion of cirrhotic patients across the studies. However, despite these differences, the studies were consistent in the finding that once weekly peginterferon is more effective than thrice weekly standard interferon alpha. In the three studies, the sustained virological response rate ranged from 30 to 39 percent among patients receiving peginterferon alpha-2a (180 µcg) compared to 3 to 19 percent among patients receiving standard interferon alpha [Evidence Grade A].

Studies on Standard Interferon Plus Ribavirin for Chronic Hepatitis C in Treatment-naive Patients

Characteristics of the studies In the fall of 2001, Kjaergard and colleagues[66] published a systematic review of the literature comparing the combination of standard interferon and ribavirin to standard interferon monotherapy. Their literature search, performed through August 2000, used MEDLINE, the Cochrane database, and manual searching. The systematic review[66] evaluated 15 randomized clinical trials of standard interferon alpha with or without ribavirin in treatment-naive patients. Among this patient group, the relative risk of not having a virological ETR with combination therapy compared to monotherapy was 0.74 (95 percent confidence interval (CI) 0.70 to 0.78) favoring combination therapy. The estimated number-needed-to-treat (NNT) to achieve an additional SVR was six among treatment-naive subjects. Patients receiving combination therapy had a higher risk of treatment discontinuation (relative risk 1.28; 95 percent

CI 1.07 to 1.52) and treatment dose reduction (relative risk 2.44; 95 percent CI 1.58 to 3.75) than did those receiving interferon monotherapy.

Four additional studies that examined the efficacy and safety of interferon alpha and ribavirin in treatment-naive patients were not included in the previously published systematic review. These studies represented a heterogeneous group with respect to treatment regimen, dose, and duration.[21,36,71,72] Evidence Table 9 summarizes the aims and eligibility criteria for these studies. El-Zayadi[71] assessed the efficacy of standard interferon alpha-2b alone and with ribavirin as initial therapy in Egyptian males with HCV genotype 4. Berg[36] examined whether 12-week combination therapy was more effective then standard interferon monotherapy in untreated patients. Ferenci[72] tested two different schedules of high-dose induction therapy with standard interferon in combination with ribavirin compared with standard interferon monotherapy. Finally, Mangia[21] compared the efficacy of high-dose interferon alpha-2b for 12 months either alone or in combination with ribavirin. The study performed by El-Zayadi included only patients with HCV genotype 4 who had HCV antibodies in the serum and an abnormal ALT. It excluded patients with decompensated liver disease, contraindications to interferon, and all other HCV genotypes. The other three studies were similar in their inclusion and exclusion criteria. They all included patients with detectable HCV in the serum and an elevated ALT. They all excluded intravenous drug users, patients with HIV infection, hepatitis B, alcohol use, decompensated liver disease, hematologic abnormalities, and major medical and psychiatric co-morbidity.

Evidence Table 10 describes the study groups and baseline characteristics of the patients in these studies. El-Zayadi compared standard interferon alpha-2b (3 MU three times per week plus ribavirin 1000 mg per day for 24 weeks) with the same dose and duration of interferon monotherapy. The percent with fibrosis or cirrhosis ranged from 27 to 30 percent. The mean age ranged from 36 to 42 years. No differences were found between the two groups. Berg compared two different induction treatments: interferon alpha-2a 6 MU three times per week for 12 weeks plus ribavirin 7 mg/kg in a divided dose twice daily for 12 weeks to interferon alpha-2a 6MU three times per week for 12 weeks. Those patients who showed a virological response to treatment were then given an additional 40 weeks of standard interferon. The average age of the patients in this study was 42 years, 55 to 57 percent were male, 11 to 13 percent had fibrosis or cirrhosis, and 73 percent in the combination group and 75 percent in the monotherapy group had genotype 1. There were no significant baseline differences in demography or clinical characteristics between the two groups. Ferenci compared three groups of patients: high dose induction, intermediate dose induction, and standard therapy. Most of the patients in the study were male, and most had HCV genotype 1. No significant differences were reported between the two groups. Finally, Mangia compared patients receiving interferon alpha-2b 5 MU three times per week for 12 months alone or with ribavirin. The mean age for the interferon alone group was 49 years, 72 were male, and 53 percent were genotype 1b. The combination therapy group had a mean age of 46 years, 61 percent were male, and 42 percent had HCV genotype 1b.

Quality of studies Evidence Table 11 summarizes our assessment of the quality of these studies. The median total quality score for the studies was 68 percent and scores ranged from 51 to 80 percent.

Results of the studies Evidence Table 12 summarizes the results of these studies. El-Zayadi found an increased biochemical SVR rate and increased virological ETR rate in Egyptian males with HCV genotype 4 who received combination therapy compared with interferon monotherapy ($p < 0.05$), but no difference in histological response. There were more adverse events reported in the combination therapy arm. Berg and colleagues found that patients receiving interferon and ribavirin induction treatment for 12 weeks compared to interferon monotherapy had a significantly greater virological ETR, but this was not sustained. Specifically, patients with genotype 1 receiving combination induction had a significantly greater response to induction than those receiving monotherapy, but at the end-of-treatment there was no difference among those with genotype 1. Ferenci and colleagues,[72] comparing different interferon induction doses, found no significant difference in biochemical or virological ETR and SR among the groups except when results were stratified by HCV genotype. They found that patients with HCV genotype 1 had a greater response to high dose induction than to intermediate dose induction or standard therapy ($p < 0.05$). Finally, Mangia, comparing interferon monotherapy to combination therapy, found that those receiving combination therapy had significantly higher virological ETR and SR.

Summary The systematic review published by Kjaergard[66] demonstrated an increased efficacy of interferon and ribavirin therapy compared to interferon alone in treatment-naive patients [Evidence Grade A]. The additional four studies were somewhat but not entirely consistent with respect to the conclusion that interferon and ribavarin is more effective than interferon alone [Evidence Grade B]. However, these studies were heterogeneous with respect to patient population and study design, which may limit the applicability of the derived data. This inconsistency may be related to the treatment protocols of these studies. The magnitude of the relative treatment effect may depend on the dose and duration of treatment.

Studies on Standard Interferon Plus Amantadine for Chronic Hepatitis C in Treatment-naive Patients

Characteristics of studies Five randomized controlled trials assessed the efficacy and safety of interferon with or without amantadine in treatment-naive patients.[25,34,73-75] Evidence Table 9 describes the aims and eligibility criteria of these trials. All of these studies included patients with detectable HCV in the serum and ALT elevation. In addition, they excluded patients with HIV (except Caronia et al),[75] hepatitis B coinfection, and major psychiatric and medical conditions,[25,34,73,74] chronic alcohol use, and active drug use. Tabon[74] specifically excluded cirrhotics.

Evidence Table 10 describes the study groups and their baseline characteristics. Helbling [73] used interferon alpha-2a 6 MU three times per week for 20 weeks, followed by 3 MU three times per week for 32 weeks, with or without amantadine 200 mg daily. Zeuzem[25] used interferon alpha-2a 6 MU three times per week for 24 weeks, followed by 3 MU three times per week for an additional 24 weeks, with or without amantadine for 48 weeks. Tabon[74] treated patients with interferon alpha-2a 6 MU three times per week for 6 months followed by 3 MU of interferon alpha-2a for six additional months with or without amantadine 200 mg daily for 12 months. Caronia[75] treated patients with interferon alpha-2a 4.5 MU three times per week for 48

weeks with or without daily amantadine 200 mg. Younossi[76] treated patients with 6 MU of interferon alpha-2a for 12 months with or without amantadine 200 mg daily.

The three studies with high dose interferon therapy followed by intermediate dose therapy [25,73,74] had similar patient ages ranging from 39 to 44 years. Helbling[73] had slightly more males than did the other two studies. In addition, the studies differed in their proportion of patients with genotype 1. Tabon[74] excluded cirrhotics. The mean age of the remaining two studies[34,75] ranged between 42[75] and 47 years.[34] In both studies, 60 to 70 percent of the patients were male. The proportions of patients with genotype 1 were 26 percent[75] and 52 to 61 percent.[34]

Quality of studies Evidence Table 11 summarizes our assessment of the quality of these studies. The total quality score for the studies ranged from 61 to 92 percent and the median score was 83 percent.

Results of studies Evidence Table 12 displays the results of these five studies. The follow-up period for these studies was 24 weeks. All three studies with high dose induction treated patients for 48 to 52 weeks. The SVR in patients receiving interferon and amantadine ranged from 10 to 29 percent. In those receiving monotherapy, the SVR ranged from 17 to 22 percent. There was no significant difference between patients treated with interferon and those receiving interferon and amantadine. Caronia[75] found no difference in sustained virological response between patients receiving interferon monotherapy versus combination therapy with amantadine. However, Mangia[34] did report a statistically significant difference between the two groups. Twenty-nine percent of those receiving combination therapy had an SVR compared with 17 percent in the monotherapy group ($p<.05$). Compared with those receiving monotherapy, patients with low baseline viral loads and genotype 1 receiving amantadine plus interferon had improved response rates.

Summary Evidence on the efficacy of interferon and amantadine was fairly homogeneous but had some methodologic limitations including varying treatment protocols. The studies were consistent in showing that interferon plus amantadine is not more effective than interferon monotherapy in treatment-naive patients [Evidence Grade A].

Q2c *What is the efficacy and safety of current interferon-based treatment options (including interferon alone) for chronic hepatitis C in selected subgroups of patients, especially those defined by the following characteristics: age less than or equal to 18 years, HCV genotype, presence or absence of cirrhosis, minimal versus decompensated liver disease, concurrent hepatitis B or HIV infection, nonresponse to initial interferon-based therapy, and relapse after initial interferon-based therapy?*

Previous Systematic Reviews

Three meta-analyses or systematic reviews[66-68] have examined randomized controlled trials of interferon alpha plus ribavirin compared to interferon alpha alone in persons who had failed to achieve a biochemical or virological response to prior interferon therapy or who had achieved a biochemical or virological response to interferon therapy followed by a relapse after treatment discontinuation.

In the systematic review discussed earlier, Kjaergard et al.[66] evaluated 15 trials including nonresponders, 10 with both relapsers and nonresponders, and one trial with relapsers and treatment-naive patients. They found that interferon nonresponders receiving interferon and ribavirin combination therapy had a 17 percent risk reduction in not achieving a virological ETR and a nine percent reduction in not achieving SVR compared with those receiving interferon monotherapy. In relapsers, combination therapy reduced the risk of not having a virological ETR or SVR by 47 percent and 38 percent, respectively, compared with interferon monotherapy.

Cummings[67] performed a meta-analysis assessing the efficacy and safety of standard interferon and ribavirin compared to interferon alone in previous interferon nonresponders. The literature was searched between January 1966 and December 1999 by means of MEDLINE and manual review of studies. Studies were included if they were randomized and compared combination therapy to monotherapy. The endpoints were ALT normalization, absence of HCV RNA, histology, and adverse events. 12 studies subsequently were included with a total of 941 patients. The pooled sustained virological response rate for combination therapy was 14 percent compared to 2 percent in patients receiving monotherapy with a risk difference of 7 percent ($p = 0.01$).

Cheng and colleagues[68] performed a literature search between January 1996 and June 2000 using MEDLINE. They included studies where treatment was at least 24 weeks, and the patients received a minimum of 800 mg of ribavirin daily and 9 MU of interferon per week. All patients had previously failed to respond to interferon. Outcomes measured were biochemical and virological ETR and SR. Seven randomized controlled trials with 766 patients demonstrated an overall weighted virological ETR of 23.1 percent with a common odds ratio of 4.9 (95 percent CI 2.9 to 8.1) in favor of combination therapy. The overall weighted SVR was 13.2 percent with

a common odds ratio of 4.9 (95 percent CI 2.1 to 11.2). The risk difference for all seven studies was 7 percent (95 percent CI 2 to13 percent).

These three systematic reviews reflected an increased SVR in previous nonresponders receiving a combination of standard interferon and ribavirin compared with those receiving standard interferon alone, although the overall response still remains low.

Twenty-three additional studies were identified that evaluated the efficacy of standard interferon and ribavirin in patients not achieving an SVR to interferon monotherapy.

Studies of Standard Interferon With and Without Ribavirin in Interferon Nonresponders

Characteristics and Quality of Recent Studies

Of the eight additional randomized controlled trials in interferon nonresponders, five studies compared combination therapy to interferon monotherapy.[32,77-80] The remainder compared different doses and/or durations of combination therapy.[19,33,81] Evidence Table 13 describes the aims and eligibility criteria. The five trials that compared the combination of standard interferon and ribavirin to standard interferon alone all required nonresponse to previous interferon therapy. Prior treatment regimens ranged from 3 MU to 6 MU of interferon for 3 to 6 months. One study [80] required nonresponse to two courses of interferon monotherapy. All of these studies excluded patients who were HIV positive, chronic alcoholics, or had hepatitis B or other causes of liver disease.

Evidence Table 14 describes the treatment groups and their demographic and clinical characteristics. The treatment regimens and study groups were heterogeneous.
Evidence Table 15 summarizes the assessment of the quality of these studies. The median total quality score was 70 percent with a range of 47 to 89 percent.

Results of Recent Studies

Evidence Table 16 summarizes the results of these studies. The study by Barbaro[77] found that the SVR in patients receiving short term beta-interferon was higher than in those receiving short term combination therapy (25 percent versus 13 percent; $p < 0.05$) at 24 weeks of follow-up. This difference was not sustained after 48 weeks of follow-up. Patients with genotype 1b receiving beta interferon had a greater SVR rate compared with the short term combination therapy group ($p = .012$). Histological improvement was also noted to be greater in patients receiving beta-interferon. The studies by Tripi[80] and Bresci[78] both reported a sustained virological and biochemical response in 6 to 7 percent of patients receiving standard interferon and ribavirin for six months. There was no difference between patients receiving interferon monotherapy and those receiving combination therapy. Combination therapy did lead to a 25 to 38 percent virological ETR, which was significantly greater than with monotherapy. Similarly, Ferenci found that 8 percent of nonresponding patients receiving high dose standard interferon and ribavirin therapy had an SVR compared to 1.5 percent of patients receiving high-dose interferon monotherapy. This difference was not statistically significant. Biochemical and virological ETR rates were significantly higher in the combination therapy group ($p < 0.05$). Finally, the study by Shiffman[32] reported that 12 to 14 percent of patients receiving combination

therapy had an SVR compared with 0 percent of patients receiving standard interferon monotherapy.

Summary

Evidence on the efficacy of standard interferon and ribavirin in nonresponders was heterogeneous and had methodologic limitations. In addition, there are differences in gender, genotype, and treatment protocols among the studies. The systematic reviews suggested a small but significant increase in sustained virological response in nonresponders receiving combination therapy. The additional studies are consistent in showing greater efficacy of combination therapy compared with interferon monotherapy in improving end of treatment response; however, this response is not consistently sustained through follow-up [Evidence Grade A].

Studies on Dose and Duration of Standard Interferon and Ribavirin for Previous Nonresponders

Characteristics and Quality of Recent Studies

The three trials[19,33,81] evaluating the optimal dose and/or duration of standard interferon and ribavirin therapy all required HCV in the serum and nonresponse to previous therapy (see Evidence Table 13). The studies by Saracco[19] and Puoti[81] excluded patients with HIV infection, chronic hepatitis B, major medical and psychiatric comorbidities, and illicit drug use. As shown in Evidence Table 14, these studies were quite heterogeneous in terms of the exact treatment regimens and characteristics of study subjects. Evidence Table 15 summarizes the assessment of the quality of these studies.

Results of Recent Studies

Evidence Table 16 describes the results of these studies. In the study by Di Bisceglie[33] 36 percent of patients with 48 weeks of therapy had SVR compared to 27 percent with 24 weeks of therapy. The statistical significance was not reported. The study by Saracco found that patients receiving 5 MU units of interferon three times per week plus ribavirin for 12 months had a significantly higher rate of SVR than those receiving 3 MU of standard interferon plus ribavirin for six months ($p < 0.05$). Finally, the study by Puoti[81] found that patients receiving daily standard interferon with ribavirin had higher rates of SVR than those receiving three times per week standard interferon ($p < 0.05$).

Summary

The studies reviewed were consistent in demonstrating increased efficacy of standard interferon and ribavirin therapy in interferon nonresponders when the dose or duration of treatment was increased [Evidence Grade B].

Studies on Standard Interferon Plus Ribavirin in Interferon Relapsers

Characteristics, Quality and Results of Recent Studies

Two studies evaluated standard interferon and ribavirin therapy for the retreatment of relapsers. The study aims varied. The study by Chapman [82] compared high-dose, long-term interferon therapy with a shorter-duration, and lower-dose of interferon and ribavirin combination therapy. The study by di Marco [83] evaluated sustained virological response in patients receiving either six or 12 months of combination therapy.

Evidence Tables 13 through 16 describe the studies' characteristics and results. Chapman's study[82] required for inclusion that patients received interferon alpha 2 MU three times per week for six months, with relapse during the 24-week follow-up period. An elevated ALT and detectable HCV in the serum were also required. The SVR after 24 weeks of follow-up was equivalent in both groups (50 percent).

In di Marco's study[83] patients were required to be positive for HCV antibodies and to have relapsed after interferon monotherapy. Patients with HIV, Hepatitis B, and major medical or psychiatric comorbid conditions were excluded. Seventy-two percent of patients receiving 12 months of therapy had an SVR, compared with 36 percent receiving six months of therapy ($p<.05$). The rate of response was higher in patients with non-1b genotype ($p<.05$).

Summary

The studies provide some evidence that longer duration of therapy with standard interferon and ribavirin but not interferon alone may have greater efficacy than shorter duration therapy in relapsers [Evidence Grade C].

Studies on Standard Interferon Plus Ribavirin in Nonresponders and Relapsers Combined

Characteristics, Quality and Results of Recent Studies

Four trials evaluated interferon and ribavirin therapy in mixed groups of relapsers and nonresponders.[84-87] These studies were heterogeneous in content. Evidence Tables 13 through 16 describe the aims, eligibility criteria, characteristics, quality, and results of these studies. In Cavalleto's study[84] patients received natural interferon 6 MU three times per week for two months followed by 3 MU three times per week for six months with or without ribavirin. Relapsing and nonresponding patients with HCV antibodies and detectable HCV in the serum were included. Patients with chronic hepatitis B, HIV, pregnancy, or decompensated liver disease were excluded. Sixty-six percent of previous relapsers had an ETR to combination therapy compared with 40 percent receiving monotherapy ($p = .02$). Sustained response (defined as both biochemical and virological) was found in 44 percent of patients receiving combination therapy compared with 16 percent in the monotherapy group ($p > .05$). In nonresponders, there was no difference in response by treatment regimen.

Enriquez' study[85] compared 24 versus 48 weeks of therapy with standard interferon alpha-2b plus ribavirin in previous nonresponders and relapsers. Patients were included if they

had HCV-RNA in their serum and an elevated ALT. Patients with cirrhosis, HIV, chronic hepatitis B, other causes of liver disease, and other major medical conditions were excluded. When results were stratified by genotype, relapsing patients with genotype 1b receiving 48 weeks of therapy had a significantly greater response than those receiving 24 weeks of treatment. This difference was not observed among nonresponders (37.1 percent of patients who completed 48 weeks of therapy compared with 15.5 percent of patients who received 24 weeks of therapy ($p = .013$)).

Min's study[86] compared high dose standard interferon plus ribavirin to a lower dose of standard interferon plus ribavirin. The study required a minimum of three months of previous interferon therapy without a sustained response. In addition, patients had to have detectable HCV-RNA in their serum and no evidence of other liver disease. The overall rate of SVR was 14 to 22 percent. The SVR rate did not differ between the two treatment groups. Relapsers, however, had a significantly greater response to therapy than did previous nonresponders ($p = .001$).

Bonkovsky's study[87] compared low-dose versus standard-dose ribavirin with standard interferon. The study required a minimum of three months of prior interferon therapy with nonresponse or relapse. The SVR in each group was 12 percent. There was no dose reduction of ribavirin in the lower-dose group.

Summary

Evidence on the efficacy of standard interferon and ribavirin in relapsers and nonresponders was heterogeneous and had methodologic limitations. The systematic review [66] suggested that combination therapy had a greater efficacy than interferon monotherapy [Evidence Grade A]. As indicated above, the additional studies were consistent in demonstrating that longer duration of interferon and ribavirin therapy has a greater efficacy than shorter duration in interferon relapsers and nonresponders. Furthermore, the evidence is consistent in showing that interferon relapsers have a better response to therapy than do previous nonresponders [Evidence Grade B].

Studies on Standard Interferon Plus Amantadine for Chronic Hepatitis C in Nonresponders

Characteristics, Quality and Results of Studies

Two trials compared interferon therapy with and without amantadine in previous interferon nonresponders.[88,89] Evidence Table 9 describes the aims and eligibility criteria. Both trials required nonresponse to previous interferon. Gaeta[88] required a minimum of four months of treatment, and Teuber[89] required a minimum of 3 months of treatment. Both excluded patients with chronic hepatitis B or HIV infection and those with decompensated liver disease. Gaeta and colleagues limited their study groups to patients with genotype 1b. Approximately 90 percent of Tueber's study population was genotype 1. Evidence Table 14 describes the baseline characteristics of the treatment groups. Evidence Table 15 summarizes the assessment of the quality of these studies.

Evidence Table 16 summarizes the results of these two trials. In neither trial was treatment with amantadine plus interferon superior to interferon alone. In fact, in Gaeta's study, the virological ETR was zero in both groups. Twenty-nine percent of the amantadine group compared with 15.8 percent of the interferon group had an end-of-treatment biochemical response, but no statistical significance was reported. Teuber and colleagues also found no significant difference in either SVR or ETR between the two treatment groups. ($p > .05$)

Summary

Evidence on the efficacy of interferon and amantadine had some methodologic limitations including differences in treatment protocols. The studies were consistent in showing that interferon plus amantadine is not more effective than interferon monotherapy in nonresponding patients [Evidence Grade B].

Studies on Standard Interferon, Amantadine and Ribavirin for Chronic Hepatitis C in Nonresponders

Characteristics, Quality and Results of Studies

Two studies evaluated standard interferon, amantadine, and ribavirin in previous interferon nonresponders.[76,90] Brillanti[90] assessed the safety and efficacy of standard interferon and ribavirin with or without amantadine. Younossi[76] compared retreatment with standard interferon and ribavirin to interferon and amantadine. Evidence Table 13 summarizes the aims and eligibility criteria of these two trials.

Brillanti and colleagues[90] included nonresponders with neither HCV-RNA clearance nor ALT normalization. Patients were required to have received standard interferon alpha 3 to 6 MU three times per week for a minimum of four months and a maximum of 12 months. Patients were excluded if they had HIV or HBV coinfection, significant medical or psychiatric comorbidities, alcoholic liver disease, or abnormal hematologic parameters.

Younossi and colleagues[76] included patients in the study if they were nonresponders to a minimum of 12 weeks of therapy. They were excluded if they were HIV positive, had decompensated liver disease, or had significant medical or psychiatric conditions.

Evidence Table 14 describes the study groups and their baseline characteristics. The assessment of the quality of these studies is summarized in Evidence Table 15.

Evidence Table 16 summarizes the results. In the small study by Brillanti et al, the SVR after six months was 48 percent in the triple therapy group, compared to 5 percent in the double therapy group ($p < .001$). Patients in the interferon/amantadine/ribavirin group also had an increase in sustained biochemical response compared to those receiving combination therapy ($p < .001$). There was no discontinuation of therapy secondary to adverse events.

Younossi found no increase in sustained virological or biochemical response in the standard interferon and amantadine group compared with the standard interferon and ribavirin group ($p > .05$).

Summary

One small study suggested that standard interferon in combination with ribavirin and amantadine may be more effective than interferon and ribavirin in nonresponders, but this conclusion is limited by the lack of genotye distribution in the countries where the studies were performed as well as lack of additional studies [Evidence Grade I].

Studies on Standard Interferon in Nonresponders and Relapsers

Characteristics, Quality and Results of Recent Studies

Eight randomized clinical trials were evaluated[23,91-97] that investigated various interferon regimens in persons who failed to achieve an SVR or SBR to a prior course of interferon therapy. These studies were heterogeneous in design and inclusion/exclusion criteria. Three studies evaluated only nonresponders to previous interferon and five studies evaluated both nonresponders and relapsers to prior interferon therapy. However, because the definition of nonresponse and relapsers varied considerably, there is a significant lack of homogeneity in the patient population studied (see Evidence Table 14). Of particular interest, one study [96] randomized persons who failed to achieve an on-treatment viral response after receiving 24 weeks of interferon alpha-2b, but who had evidence of a histological response by liver biopsy performed after six months of interferon, to receive continued interferon alpha (i.e., maintenance therapy) versus observation. Whereas the majority of studies sought to evaluate biochemical or viral response, the primary aim of this study was to evaluate progression of liver histology as determined by comparison of the first liver biopsy to a second biopsy performed after 24 months of continued therapy or observation. One study [23] evaluated the effect of longer duration of interferon therapy (6 versus 12 months) compared to higher dose of interferon (3 MU versus 10 MU) in relapsing patients.

There was also significant heterogeneity in the interferon regimens among studies (see Evidence Table 14). Several studies evaluated higher doses of interferon (e.g., > 3 MU) or greater frequency of administration (e.g., daily versus three times per week) or different types of interferon (e.g., interferon alpha-2a and-2b, alphacon1, lymphoblastoid interferon, and natural interferon). The clinical and demographic features of the study populations were also heterogeneous. One study [96] compared continued or maintenance interferon alpha-2b 5 MU three times per week to no treatment among histological responders to prior interferon. The study population was half male, white and had evidence of elevated serum ALT and hepatic fibrosis on liver biopsy.

Study quality was varied (Evidence Table 15). In general, among nonresponding patients, these studies demonstrated low rates of biochemical and/or virological response to retreatment with interferon-based regimens, whereas among relapsing patients, virological and biochemical responses were typically higher than those observed in nonresponders. Among interferon nonresponders, one study [96] demonstrated that continued interferon alpha-2b for 24 months was associated with the maintenance of histological benefit observed at study entry. Patients who received maintenance interferon had lower hepatic inflammation and fibrosis scores over time than did those who discontinued therapy despite persistent viremia, a finding that suggests long-term interferon therapy may be associated with histological benefit. Among interferon relapsers,

one study [23] demonstrated higher rates of SVR among patients who received longer duration (12 months) of low-dose interferon (3 MU) [SVR, 32 percent] compared to those who received shorter duration (6 months) of either low-dose (3 MU) [SVR, 14 percent] or higher-dose (10 MU) [SVR 17 percent] interferon. Consequently, among relapsers the duration of retreatment may be of greater importance than the dose delivered.

Summary

Evidence of the efficacy of interferon monotherapy was heterogeneous and had important methodologic limitations. The studies were consistent in showing that interferon monotherapy is relatively ineffective in the retreatment of nonresponders and relapsers [Evidence Grade B]. However, one study suggested histological benefits may be achieved in some nonresponding patients assigned to "maintenance" interferon, and a second study suggested duration of therapy in relapsing patients is an important predictor of sustained viral response.

Standard Interferon Therapy in Subgroups

Characteristics, Quality and Results of Recent Studies

Five studies met inclusion criteria for review in clinically important subgroups.[20,31,98-100] Two of these studies reported information on race,[20,98] one reported on patients with end stage renal disease requiring hemodialysis,[99] one studied hemophiliacs, and one studied hepatitis B and hepatitis C co-infected patients. Evidence Tables 13 through 16 summarize the characteristics and results of these studies.

The two studies reporting on race were subgroup analyses of large randomized controlled trials. The first[20] reported the results of two randomized controlled trials[101,102] and stratified outcomes by race. Reddy and colleagues[98] retrospectively analyzed data from the consensus interferon trial and stratified outcomes by race. McHutchinson[20] found that blacks had no response to interferon monotherapy compared with 13 percent of whites. In contrast, 20 percent and 23 percent of blacks responded to interferon plus ribavirin for 24 or 48 weeks, respectively. However, this response was lower than that of whites (32 percent and 42 percent respectively). When patients were analyzed by genotype, the researchers they found that Blacks and whites with genotype 1 had similar responses to combination therapy, whereas blacks with genotype 1 did not respond to interferon monotherapy.

Reddy and colleagues[98] found that blacks had significantly lower end-of-treatment biochemical and virological response than did whites. The rate of SVR was 12 percent in whites and 2 percent in blacks, but this did not reach statistical significance ($p = .07$). Multivariate analysis demonstrated that non-1 genotype predicted response to interferon.

Campistol and colleagues[99] performed a multicenter randomized controlled trial assessing the efficacy and tolerance of interferon alpha-2b in the treatment of chronic hepatitis C in patients undergoing hemodialysis. In the treatment group, 14 of the 19 patients had an ETR, and 42 percent (8/19) had a sustained response at two years. Treatment was discontinued in 10 out of 19 patients in the treatment group secondary to leucopenia in (three patients), anemia (1), diarrhea (1), and depression (1). Ten patients in the treatment group and five patients in the

control group underwent cadaveric renal transplant. Decreased ALT observed during treatment was also observed after transplant.

Rumi[100] reported on hemophiliacs randomized to either interferon alpha-2b 3 MU three times per week for six months or to the control group. Some 13 percent of patients treated with interferon had a complete biochemical and virological response at the end of 24 weeks of follow-up. This percentage was significantly greater than in the control group ($p < .01$). In conclusion, the response rate to interferon monotherapy in hemophiliacs is similar to that observed in persons without hemophilia.

Villa et al.[31] studied the effect of interferon in patients with hepatitis B and hepatitis C co-infection. They found that the virologic ETR of patients receiving 6 MU of interferon compared to that of those receiving 9 MU of interferon three times per week for six months was 86 percent and 75 percent, respectively. There were only 30 subjects in this study, thus limiting the generalizability of the results.

Relation Between HCV Genotype and Treatment Effect on SVR

Ten studies reported enough data to permit a multivariate logistic regression analysis of the relation of HCV genotype to the effect of treatment on the SVR rate (see Table 2 at end of chapter). The resulting analysis indicated that HCV genotype 1 generally was associated with a lower SVR rate than other genotypes. However, the analysis were relatively consistent in showing that were was no interaction between HCV genotype and the effect of different treatment regimens on the SVR rate. This suggests that the most efficacious treatment was the same for those with and without HCV genotype 1 despite having a lower SVR rate with genotype 1 than other genotypes.

Summary

Evidence on the efficacy of interferon in subgroups was heterogeneous and had important methodologic limitations [Evidence Grade I]. Evidence suggested that blacks respond differently to interferon monotherapy than do whites. One randomized controlled trial in renal patients presented evidence that patients on dialysis may respond to interferon therapy and that this response may be sustained post transplant. While encouraging, this one small study does not provide conclusive evidence of this phenomenon. One study suggested that standard interferon may have a small effect in hemophiliacs, and one study suggested that standard interferon may lead to virologic ETR in patients with both hepatitis B and C. There are important limitations to these findings. Because randomized controlled trials in these subgroups are few, generalizable conclusions are difficult to make. Despite the relatively high prevalence of HCV coinfection among HIV-infected persons, no randomized controlled trials were available to address the safety, efficacy and tolerability of standard interferon alpha or interferon alpha plus ribavarin in this population.

Q2d What are the long-term clinical outcomes (greater than or equal to 5 years) of current treatment options for chronic hepatitis C?

Results of the Literature Search

Forty studies ultimately met the criteria for question 2d. These studies were heterogeneous in study design, eligibility criteria, patient characteristics, and outcomes. Studies included were randomized controlled trials, prospective and retrospective cohorts and case series. Evidence Tables 17 through 20 summarize these features. Of the 40 studies, 17 assessed long-term outcomes of chronic hepatitis C in patients treated with interferon. The remaining 23 studies addressed the natural history of hepatitis C and either did not explicitly indicate whether treatment was received by any of the patients or stated that all patients were untreated. Twenty-five studies were performed at tertiary care centers. Seven were evaluated on community based cohorts and eight studies were unclear as to the source of patients.

Long-term Outcomes of Interferon-based Therapy

Characteristics of studies In the studies including interferon-treated patients in the assessment of long-term outcomes of chronic hepatitis C, progression of liver disease was measured in terms of the incidence of cirrhosis (three studies), HCC (15 studies), incidence of resectable HCC (two studies), hepatic decompensation (two studies), overall and liver-related mortality (two studies), liver transplantation (two studies), and SVR (two studies). Inclusion and exclusion criteria among these studies were fairly heterogeneous (Evidence Table 17). In most studies, patients had to have a liver biopsy and be HCV seropositive to be included. In addition, patients with chronic hepatitis B generally were excluded from these studies. The studies were inconsistent in their inclusion or exclusion of alcoholics, cirrhotics, and intravenous drug users. One study did not mention any eligibility criteria.[103]

As indicated in Evidence Table 18, the study designs were predominantly prospective and retrospective cohort studies, although there were a few randomized controlled trials.[104-106] The treatment protocols were highly variable ranging from daily standard interferon for two weeks[103] to every other day for six to 12 months. The majority of studies reported only partial details of the treatment regimens. Either interferon duration or frequency was not mentioned. A few studies mentioned only the numbers of patients receiving interferon in the cohort. In addition, members of individual cohorts may have received varying frequency, dose, or duration of therapy. The baseline characteristics of participants in these studies also varied. All of these studies included both men and women with a range of hepatitis C genotypes and histologic findings on liver biopsy. In many studies, racial and ethnic characteristics were not presented . The mean age ranged from 35 to 58 years old. The percentage of patients with cirrhosis in these studies ranged from 0 to 100 percent. The percentage of patients with alcohol consumption ranged from 0 to 49 percent, with alcohol consumption being defined differently across the studies.

Quality of studies Evidence Table 19 summarizes the assessment of the quality of these studies. The quality score for the cohort studies ranged from 35 to 90 percent. In general, these studies received higher scores in the representativeness and statistical analysis categories and lower scores in the bias and confounding category. Very few studies reported on the type or degree of involvement of the funding source. The quality score for the randomized controlled trials was 69 percent or greater. These randomized controlled trials had quality scores greater than or equal to 75 percent for the main study quality categories, except for the categories of bias and outcomes assessment in the study by Bernardinello [104]. The studies did not report the type or degree of involvement of the funding source.

Results of studies Four retrospective cohort studies stratified the reporting of outcomes by response to interferon therapy. Horiike [103] and colleagues compared patients who had a complete biochemical and virological response to standard interferon both to nonresponders and to those receiving no therapy. The authors found an annual incidence of HCC of 0 percent, 0.3 percent and 1.6 percent, respectively, ($p < 0.05$ comparing treatment versus no treatment) and an overall incidence of HCC of 0 percent, two percent, and 15 percent. When they further stratified their results by histology, they found that those untreated with F3 histology had a significantly greater incidence of HCC than did complete responders and nonresponders combined (36 percent versus 0 percent; $p < 0.05$). In contrast, Shindo [107] found the annual incidence of cirrhosis to be significantly higher in nonresponders than in relapsers or patients who had a biochemical response or complete response (15 percent versus 1 percent, 0 percent and 0 percent; $p < 0.001$). Moreover, they reported the annual incidence of HCC to be 6 percent in nonresponders, which was significantly higher than in all other study groups ($p = 0.0001$) except for the untreated controls. Tanaka[108] reported the risk of developing HCC seven years after standard interferon therapy and found the risk to be 17 percent in untreated controls versus 12 percent in those treated, regardless of response ($p = .076$). The annual incidence of HCC in patients having a biochemical sustained response was 0.35 percent and in relapsers it was 0.63 percent; by contrast it was 2.1 percent in nonresponders. The seven year cumulative risk of HCC was significantly greater in nonresponders than in relapsers and patients having a biochemical sustained response (22.4 percent versus 3.7 percent and 1.2 percent, respectively; $p < 0.01$). Multivariate analysis demonstrated that the risk ratio for developing HCC in sustained and transient responders versus controls was 0.16 ($p = 0.007$) and 0.27 ($p = 0.02$), respectively. Yabuuchi[109] reported the five year cumulative incidence of HCC to be 2.3 percent in complete responders, 2 percent in biochemical responders, and 14.3 percent in nonresponders ($p < 0.05$ for the comparisons to nonresponders).

Four studies, performed in tertiary care centers, stratified outcomes by treatment or control group. Inoue[110], in a retrospective study that excluded cirrhotics, reported the five year cumulative incidence of HCC as 2.2 percent in patients treated with standard interferon, compared with 9.5 percent in untreated patients with chronic hepatitis C ($p = 0.0015$). A Cox proportional hazard model adjusted for age, gender, ALT, platelet count, and AFP level found a 69 percent decrease in risk of HCC in patients receiving standard interferon ($p = 0.015$). Nishiguchi et al.[111] prospectively compared 90 cirrhotic patients randomized to standard interferon or symptomatic treatment. After nine years the incidence of HCC was 27 percent in interferon-treated patients versus 73 percent in untreated controls ($p < 0.001$). By multivariate

analysis the risk ratios of those treated were 0.26 for the development of HCC and 0.14 for death. Moreover, they found that as ALT increased, the risk of HCC increased. Bernadinello[104], in a randomized trial, compared three months of standard beta-interferon with no treatment and found no difference in SVR, the incidence of HCC, or the incidence of hepatic decompensation at five years among cirrhotic patients. Fattovich[5] compared treated and untreated cirrhotics with standard interferon and found a significant decrease in hepatic decompensation in those treated with interferon ($p < 0.01$) but no difference in HCC incidence over five years.
An additional two studies reported long-term outcomes by dose or duration of standard interferon treatment. In a randomized trial, Chemello et al[105] compared a daily dose of standard interferon for three months followed by three times a week dosing to six months of three times a week standard interferon and found no difference in viral or biochemical sustained response after 72 months. Toyoda[112] retrospectively looked at noncirrhotic relapsers and nonresponders who received more than 500 MU of standard interferon versus less than 500 MU of interferon. The overall incidence of HCC was 5.5 percent at a mean of 60 months. They found no difference in the rate of HCC by duration of therapy, but did find a significant difference in rate of HCC by dose of therapy. Those patients with higher doses of interferon had a lower incidence of HCC ($p < 0.05$). Moreover, total dose of interferon was an independent predictor of HCC. Ikeda[113] retrospectively compared untreated controls with patients receiving less than 12 months of standard interferon and greater than 12 months of standard interferon. He found the ten-year incidence of HCC to be significantly less in patients receiving longer courses of interferon therapy (21 percent) than in those receiving short-term therapy (65 percent) or those untreated (47 percent; $p < 0.05$). The ten year survival was 93 percent in the long-term interferon group compared with 68 percent in the short-term interferon group and 57.4 percent in the untreated group ($p < 0.01$ for the comparison to the untreated group).

The six remaining studies did not stratify outcomes by treatment received or treatment response but indicated that a portion of patients in the cohort underwent therapy. Yatsuhashi[114] followed 186 individuals prospectively and found the cumulative probability of developing HCC at 15 years to be 45 percent. They found fibrosis stage and age greater than 50 years to be risk factors for the development of HCC. Inflammatory activity and treatment status were not independent risk factors for HCC. Aizawa[115] retrospectively studied 153 men and women with chronic hepatitis C and found the cumulative incidence of HCC at 15 years to be 42 percent and the annual incidence to be 2.8 percent per year. Factors predictive of HCC included older age, habitual heavy drinking, and histological stage. Forty-five percent of patients with severe fibrosis at initial biopsy developed HCC at 13 years compared with 23 percent of patients with mild fibrosis at initial biopsy ($p < .01$). Kobayashi[116] retrospectively studied 61 patients consecutively treated with standard interferon for six months and found that patients with serum ALT less than 75 U/L had improved liver histology over five years compared to patients with an ALT greater than 75 U/L, who had worsened histology. Bruno[117] prospectively studied 163 Child's class A cirrhotics and found the incidence of HCC to be 13.5 percent at a median of 68 months of follow-up. In addition, 86 percent of these patients had genotype 1b. Only 18 percent of cases of HCC were resectable. The total mortality in this group was 13.5 percent, and 50 percent of these deaths were related to hepatitis C. The incidence of liver transplantation was 1.2 percent. Benvegnu[118] investigated the relation between HCV genotype and HCC in cirrhotic

patients and found the incidence of HCC over a mean time of 66.9 months to be about 21 percent. The incidence was not significantly different among HCV genotypes. Hepatitis C-specific mortality was 22 percent. Those with mixed HCV genotype had significantly more deaths than those with genotype 2 (66 percent versus 16 percent; $p < 0.05$). The incidence of liver transplantation was 1.25 percent. Shibata[119] compared untreated cirrhotics to treated noncirrhotics and found the incidence of HCC to be 52 percent versus 6.2 percent, respectively ($p < 0.01$).

Summary of studies on long-term outcomes of interferon-based therapy The evidence on the effect of standard interferon on long-term outcomes in chronic hepatitis C was heterogeneous and had important methodologic limitations. The studies were primarily retrospective and prospective cohorts. Retrospective studies are limited in their ability to determine the effect of interferon on outcomes secondary to selection bias. In these cohorts, interferon-treated patients were neither randomly selected nor selected by strict criteria. Thus, despite multivariate analysis with adjustment for confounders, there is residual bias toward a positive treatment effect. Consequently caution is necessary when interpreting retrospective cohorts. Long-term outcomes of randomized controlled trials would be ideal. Other limitations include variable lengths of follow-up within and among studies, variable numbers of patients with cirrhosis at baseline, different doses and durations of therapy (frequently missing details about dose and duration), varying amounts of alcohol consumption, and little description of the population that was not treated.

These studies nonetheless were somewhat consistent in suggesting that treatment with standard interferon-based therapy produces a moderate decrease in the risk of HCC and cirrhosis in complete responders [Evidence Grade B]. The evidence also suggested that patients having a biochemical response to standard interferon may have a decreased risk of HCC and progression of liver disease [Evidence Grade B]. However, the data were inconsistent regarding the impact of standard interferon therapy on long-term outcomes in nonresponders and relapsers compared to untreated patients. One long-term randomized controlled trial suggested that all patients treated with standard interferon, regardless of response, derived long-term benefits; other studies suggest that relapsers but not nonresponders may derive some long-term benefit from standard interferon therapy [Evidence Grade C].

Long-term Outcomes of Chronic Hepatitis C in Untreated Patients

Overview of characteristics of the studies Twenty-three studies addressed the long-term natural history of chronic hepatitis C. Table 17 summarizes their aims and eligibility criteria. Because of our selection criteria, all of these studies had a mean or median follow-up time of at least five years. Long-term outcomes mentioned in the objectives included histologic progression and hepatitis C-related morbidity and mortality. The patients followed were heterogeneous across studies as were the inclusion and exclusion criteria. Three studies described the natural history of hepatitis B and C in cirrhotics [120-122]; one study described the natural history of hepatitis B and C in noncirrhotics[123]; two studies prospectively looked at the progression of liver disease in patients with hepatitis C who had persistently normal serum ALT[124,125]; three studies assessed long-term outcomes in renal patients who had chronic hepatitis C[126-128]; three studies looked at patients with HIV and HCV co-infection[129,130,133]; two studies

focused only on patients with hepatitis C secondary to transfusion [131,132]; two studies looked primarily at intravenous drug users[133,134]; two studies looked at long-term progression of chronic hepatitis C by HCV genotype[135,136] and another by initial biopsy alone[137]; one study looked at patients with coagulation disorders and chronic hepatitis C[138]; one study looked at women with hepatitis C after receiving contaminated anti-d-immunoglobulin[139]; and finally, there were two miscellaneous cohort studies[140,141]

Characteristics and results of studies in patients with chronic hepatitis B and hepatitis C co-infection Chiaramonte[120], Gentilini[121], and Ikeda[122] looked at long-term outcomes in cirrhotics with hepatitis B or C. Although Chiaramonte and Ikeda included patients with hepatitis B and C co-infection, such patients were excluded from Gentilini's study. As shown in Evidence Table 17, exclusion criteria for Chiaramonte and Gentilini were otherwise similar in that those with alcoholic or decompensated liver disease were not included in the analysis. Ikeda excluded patients with portal hypertension, Budd-Chiari syndrome, subacute hepatitis or chronic aggressive hepatitis, but 65 patients had decompensated cirrhosis with ascites, history of encephalopathy, or both. The mean age of patients in these three studies ranged from 50 to 54 years. The percentage of men in the studies ranged from 57 percent to 78 percent.

The total study quality scores for the studies by Chiaramonte and Gentilini were 51.9 and 41 percent, respectively. They both received low scores for the description of therapy because they did not explicitly report whether patients received any primary or ancillary form of treatment.

Chiaramonte found the 10-year cumulative incidence of HCC to be 45 percent in patients with co-infection, and 28 percent in patients with hepatitis C alone. Factors predictive of HCC in Chiaramonte's study included hepatitis B and C co-infection, male gender, and age greater than 50 years. Gentilini reported the overall incidence of HCC to be 8.6 percent and the hepatitis C-related mortality to be 19.2 percent. Ikeda found the 10-year incidence of HCC in patients with hepatitis C to be 53.2 percent and 27.2 percent in patients with hepatitis B ($p = 0.003$). Risk factors for HCC in patients with HCV infection were age, AFP level, and previous alcohol intake. Risk factors for HCC in patients with HBV infection were age and findings on indocyanine green test. These three studies in cirrhotic patients suggested different rates of hepatocarcinogenesis between patients with HBV and those with HCV infection.

One study[123] retrospectively compared the incidence of HCC in non-cirrhotic patients with chronic hepatitis C versus hepatitis B. Patients were included if they had chronic persistent hepatitis or chronic active hepatitis on biopsy. Patients were excluded if they had co-infection with hepatitis B and C, an elevated AFP, or HCC. The mean age of patients with HBV infection was 33.2 years versus 49.6 years in patients with HCV. Eighty percent of the patients with HBV infection were male compared with 77 percent of the patients with HCV. The total study quality score was 65 percent. The incidence of HCC in patients with hepatitis C was 10.5 percent at a mean follow-up of 73 months compared to 3.9 percent in patients with hepatitis B at a mean follow-up of 73 months ($p < 0.05$). Moreover, for patients with chronic hepatitis C, the more histologically advanced the disease the shorter the time to HCC.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C by ALT level Two prospective cohort studies assessed the relation of serum ALT levels to long-term outcomes in untreated chronic hepatitis C. Persico[124] followed 37

asymptomatic patients with hepatitis C with persistently normal ALT. Hayashi[125] compared outcomes in patients with normal ALT, intermittently abnormal ALT, and always abnormal ALT. Both studies required positive HCV antibodies and excluded patients with hepatitis B. Persico additionally excluded intravenous drug users and patients with fibrosis. The two study populations also differed in location, as Persico's was conducted in Europe and Hayashi's in Japan. Finally, the two studies differed in the distribution of HCV genotype. Persico's study included primarily patients with genotypes 2a and 1b, while Hayashi's included patients with HCV genotype 1a. The total study quality scores of the studies were 71 and 80 percent as indicated in Evidence Table 19. The study by Hayashi received a low score for its reporting of outcomes. Persico found no significant change in histology in the patients with a sustained normal ALT. Hayashi reported no cases of HCC in patients with normal ALT levels. In contrast, patients with always abnormal ALT levels had a 31 percent five year incidence of HCC.

Characteristics and results of studies on long-term outcomes of untreated chronic Hepatitis C in patients with renal disease One study[126] prospectively followed three groups of patients: one group on hemodialysis with hepatitis C; one group on hemodialysis without HCV; and one group with HCV not on hemodialysis. The inclusion and exclusion criteria were not reported explicitly. The mean age was 58.9 years, 58 percent were male, and none used greater than 60 grams of alcohol per day or illicit drugs. Ultrasound imaging of the liver showed that HCV-positive patients on hemodialysis had a greater frequency of both coarse and nodular patterns than those without hepatitis C viremia (coarse in 51.3 percent versus 31.4 percent, $p < 0.05$; nodular in 21.3 percent versus 3.9 percent, $p = 0.0001$). In addition, most patients with HCV and on hemodialysis in this cohort had a normal ALT. The annual incidence of HCC was 0.53 percent and occurred only in HCV-positive patients.

Two retrospective cohort studies were performed looking at the effect of HCV after a renal transplant. The general aims were different for these two studies. Rostaing and colleagues [128] looked at the effect of immunosuppression on liver histology in renal transplant patients, while Kliem [127] assessed the impact of hepatitis C on morbidity and mortality post transplant. Renal transplantation and immunosuppressive therapy were inclusion criteria for both studies. As shown in Evidence Table 19, the study quality scores for the Rostaing study were lower than the scores for the Kliem study.

Rostaing found on biopsy that most of the transplant patients had chronic hepatitis and the mean Histology Activity Index was 6. They also found that the serum HCV RNA levels were high at the time of biopsy, an elevation they felt might be related to immunosuppression. Kliem concluded that there was a low morbidity related to hepatitis C in renal transplant patients, but hepatitis B co-infection and hemodialysis increased the risk of chronic liver disease in these patients.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C in patients with HIV infection Two studies followed patients with HIV infection and chronic hepatitis. These studies were heterogeneous in their study groups and aims (see Evidence Table 17). One study compared HCV negative and HIV positive hemophiliacs with HCV positive, HIV negative hemophiliacs[129]. The other study compared HIV and HCV co-infected patients treated with or without protease inhibitors[130].

Lesens[129] compared HIV and HCV co-infected hemophiliacs to those with HCV alone. The only stated inclusion criterion was detectable HCV in the serum. The total study quality score was 42.8 percent. All patients had hemophilia A or B. The mean age at infection was 19.7 years in the co-infected group compared to 22.2 years in the HCV-alone group. One patient in the co-infected group also had HBV infection. The rate of progressive liver disease was 27 percent in the co-infected group compared with 6 percent in the HCV-alone group. The mean time to progressive liver disease was 17 years. The hepatitis C-specific mortality rate was 8.6 percent in the co-infected group versus 0 percent in the HCV-alone group. This study provides some evidence that HCV and HIV co-infection leads to a more rapid progression of liver disease.

The second study[130] assessed the effect of protease inhibitors on liver fibrosis in patients co-infected with HIV and HCV. Patients were included in this study if they had HCV in their serum, HIV infection, and had used antiretroviral therapy. Patients were excluded if they had hepatitis B or received immunosuppression. The mean age was 37 years. All of the patients in the non-treatment group were males compared with 60 percent in the treatment group. Most of the patients were infected through intravenous drug use. The study's quality scores are shown in Evidence Table 19. The rate of progression of liver fibrosis was 1.36 percent per year in the treatment group compared with 2.1 percent per year in the no treatment group ($p < 0.05$). In addition, 29 percent of patients not receiving treatment progressed to cirrhosis compared to 6.3 percent of patients receiving protease inhibitors ($p < 0.01$). Cirrhosis was higher in patients drinking greater than 50 grams per day of alcohol, patients older than 20 years at the time of HCV infection, patients who had never received protease inhibitors, and patients with low CD4 counts ($p < 0.05$).

Characteristics and results of studies on long-term outcomes of chronic hepatitis C in patients with a history of blood transfusion Two studies reported long-term outcomes in transfusion recipients with HCV infection. Harris[131] performed a retrospective cohort study comparing transfusion recipients infected with HCV with those who were HCV negative. Patients were excluded if they were exposed to any other blood products, used intravenous drugs, or were transfused after being tested for HCV. The total study quality score was 70 percent. After the first decade of infection, the hepatitis C-specific mortality was 1 percent in those infected with HCV. Furthermore, they found that infected patients had an increased risk of death with high levels of alcohol consumption.

Murakami and colleagues[132] performed a prospective cohort study of patients with transfusion-related HCV. Patients were included in the analysis if they had detectable HCV in the serum, positive HCV antibodies, and no history of antiviral therapy. They were excluded if they had hepatitis B, intravenous drug use, greater than 80 grams of alcohol intake daily for the past three years, or other causes of liver disease. The incidence of cirrhosis was 23 percent. The mean time to cirrhosis was 6.5 years less for those transfused after 50 years of age compared to all other ages and was 19.8 years less for those transfused in their forties compared to all other ages. As age at time of transfusion increased, the cumulative incidence of HCC increased ($p < 0.001$).

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C in patients who use intravenous drugs Thomas[133] prospectively studied the natural history of hepatitis C in a cohort of intravenous drug users. Patients were included in the cohort

if they were older than 17 years, used intravenous drugs, and were positive for HCV antibodies. The population was primarily African American; 78 percent were male and 73 percent earned less than $5,000 per year. One third were HIV infected and two percent used alcohol. Sixty percent had HCV genotype 1a. Over a median follow-up of eight years, the incidence of cirrhosis in this population was 3.3 percent and the incidence of decompensation was 2.4 percent per year. In this study, 5.4 percent of patients spontaneously cleared their virus and the hepatitis C specific mortality was two percent.

Rodger[134] followed a cohort of intravenous drug users with 35 HCV positive individuals and 70 HCV negative controls available for follow-up. The study quality scores were low (see Evidence Table 19), and many of the cases of HCV infection were not reported from this cohort. However, there were no cases of HCC over this time, and only two cases of cirrhosis.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C by HCV genotype Two studies measured long-term outcomes of chronic hepatitis C by HCV genotype [135,136]. Kobayashi[135] retrospectively studied patients with either HCV genotype 1 or genotype 2 to assess if long-term outcomes differed by genotype. Inclusion criteria included an abnormal serum ALT and age between 18 and 60 years. Patients were excluded if they consumed more than 80 grams of alcohol per day, had received antiviral therapy, were HIV positive, or had evidence of hepatitis B. The two groups were equivalent in terms of gender, age, histology, and hepatic transaminases. The total study quality score was 92.7 percent. The incidence of HCC in patients with HCV genotype 1 was 29 percent, and in genotype 2 it was 5.5 percent ($p < 0.01$). In addition, patients with HCV genotype 1 had greater deterioration in grade and histology than those with genotype 2, and their mean HCV titer was significantly higher ($p < 0.001$).

Matsumura[136] studied the progression of chronic hepatitis C by HCV genotype. Patients were included if they had an abnormal serum ALT and positive serum HCV. The patients were excluded if they had hepatitis B or an autoimmune disease. The total study quality score was 75 percent. The mean age was 50 years, and 61 percent were male; 53 percent had received blood transfusions. The mean overall rate of progression per year of liver fibrosis was 0.12 percent for patients with F1, F2, F3, and F4 histology. There was no difference among patients with HCV genotypes 1b, 2a, or 2b. However, when rate of progression was broken down according to age of transfusion (greater than or less than 30 years old), the rate of progression of liver fibrosis for men and women with HCV genotype 1b was greater for patients transfused after the age of 30 years ($p = 0.001$). Multivariate analysis demonstrated that increased age and low platelet count were risk factors for HCC.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C by histology Yano[137] retrospectively assessed the pathologic evolution of HCV infection over time in 70 patients. Patients with a history of previous therapy, immune suppression, cirrhosis, hepatitis B infection, and habitual heavy drinking were excluded. An initial liver biopsy and HCV antibodies were required for inclusion. The population was predominantly male and Asian, and all patients had fibrosis. The total incidence of cirrhosis in this population was 50 percent. The initial presence of high grade or stage on biopsy predicted accelerated progression to cirrhosis.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C in patients with coagulation disorders Meijer[138] studied the natural history of hepatitis C in HIV-negative patients with coagulation disorders. The mean age of this cohort was 40 years old, 96 percent were male. The total study quality score was 68.5 percent. Thirty patients had hemophilia A, and 14 patients had hemophilia B. After a median of 19 years of infection, 16 percent had cirrhosis by ultrasound and only 4 percent of patients had symptomatic disease.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C in women who acquired HCV through contaminated anti-d-immunoglobulin Barrett[139] prospectively followed a cohort of Irish women infected with genotype 1 HCV during pregnancy as a result of contaminated anti-d-immunoglobulin. The study quality score was 56.2 percent. In 22 years of follow-up, there were no cases of HCC or cirrhosis. Ten women with hepatitis C did acquire mixed essential cryoglobulinemia.

Characteristics and results of miscellaneous other studies on long-term outcomes of untreated chronic hepatitis C Forns[141] followed a cohort of Spanish patients with chronic hepatitis C for more than 20 years. Patients were excluded if they had hepatitis B, cirrhosis, greater than 40 grams per day of alcohol intake, or autoimmune disease. This retrospective cohort study had a high total study quality score. Fifty-nine percent of patients were male, and the mean age was 43 years. Over this 20-year period, 39 percent of patients developed cirrhosis, 10.5 percent developed hepatic decompensation, and 7 percent developed HCC. The all-cause mortality rate was 22 percent, and the hepatitis C-specific mortality was 6 percent.

Punyagupta[140] assessed the long-term outcomes of Thai patients with hepatitis C. The study sample was 55 percent male and 9 percent had cirrhosis. The overall incidence of HCC in this population was 16 percent. Sixty percent of the patients with chronic hepatitis C were deceased at ten years, and 85 percent were deceased at 15 years.

Summary of Studies on Long-term Outcomes in Untreated Patients

The evidence on the natural history of chronic hepatitis C suggests that older age, cirrhosis, hepatitis B infection, HIV infection, alcohol use, male gender, and initial fibrosis all predict long-term outcomes in hepatitis C [Evidence Grade B]. This evidence is heterogeneous and does have methodologic limitations. Nevertheless, the studies are consistent in showing that these variables predict long-term outcomes.

The evidence of the effect of HCV genotype on the natural history of hepatitis C is based on two studies with relatively high study quality scores. The results of these studies are not consistent with each other. One study (with the highest quality score) suggested that HCV genotype 1 was associated with an increased risk of HCC and progressive liver disease, but the other study did not find a significant relationship between HCV genotype 1b and the risk of hepatocellular carcinoma or progressive liver disease [Evidence Grade I].

The evidence of the effect of hepatitis B infection on the natural history of hepatitis C is limited, but suggests that concurrent hepatitis B infection significantly increases the risk of HCC in patients with chronic hepatitis C [Evidence Grade C].

The evidence on the relation of serum ALT to long-term clinical outcomes in patients with untreated chronic hepatitis C is based on two studies, one of which is rather small. The two

studies agree that the risk of HCC is very low in patients with normal ALT levels [Evidence Grade B]. One of the studies also suggests that the risk of HCC increases significantly when the ALT is persistently elevated.

Q3a What is the efficacy of using screening tests for HCC to improve clinical outcomes in patients with chronic hepatitis C?

Incidence of HCC

Hepatocellular carcinoma is one of the most common cancers in the world. Incidence rates vary from continent to continent with the highest rates reported in Asia at 80 per 100,000.[142] Chronic hepatitis B and C have been linked as major factors increasing the risk of HCC. The incidence of HCC in patients with hepatitis B is as high as 0.46 percent per year[143-146] whereas the incidence in patients with hepatitis C may range between 0 percent and 1.6 percent per year.[103]

Several studies in our review of key question 2d demonstrated risk factors for HCC, including male gender, alcohol use, older age at which HCV was acquired, duration of infection, cirrhosis, alcohol abuse, and hepatitis B or HIV co-infection.

Screening for liver cancer is very controversial. There have been no randomized controlled trials of screening a cohort of hepatitis C patients for HCC. In addition, few studies have evaluated the cost, efficacy, and potential benefit.

Unlike hepatitis C, a number of screening and cohort studies have been reported for hepatitis B with varying results. For example, using AFP as a screening test, a study of 1,400 hepatitis B patients in Alaska detected 15 tumors, of which ten were resectable.[145] Another study prospectively screened 1,069 HBV carriers for 6 months to 6 years, and over this period detected 15 tumors, seven of which were resectable.[146]

Results of Literature Search on Outcome of Screening for HCC

Through the abstract review process we identified 40 articles that could have data on one of our key questions about screening for HCC in patients with chronic hepatitis C. After reviewing these 40 articles as well as all of the references for all articles pertaining to screening for HCC, we found one study that answered question 3a regarding outcomes with screening for HCC at entry into the study.[147]

Characteristics of the Study on Outcomes of Screening for HCC

Evidence Table 21 summarizes the aims and eligibility criteria of this study. The study population was remarkable for including patients with chronic liver disease, regardless of etiology, and included cirrhotics as well as noncirrhotics. The studied excluded patients with HCC at entry.

Quality of Study

As shown in Evidence Table 22, the overall quality score for this study was 70 percent with scores of 100 percent in representativeness and description. The low scores were 33 percent in statistics, 50 percent in bias and 65 percent in outcomes. This study did not report the source of funding or the type and degree of involvement of the funding agency.

Results of the Study on Outcomes of Screening for HCC

The one study[147] for question 3a was a prospective cohort analysis evaluating the efficacy of HCC screening in patients with cirrhosis or chronic hepatitis without cancer at one study center compared to patients with cirrhosis or chronic hepatitis followed in another hepatitis clinic.(Evidence Table 24) Three hundred sixty subjects with chronic liver disease were enrolled and received an ultrasound study of the liver as well as measurement of serum AFP and liver function parameters (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubins, coagulation studies, and albumin) every 6 months. This group was compared to a population of 2,170 patients with histologically documented cirrhosis or chronic hepatitis who did not undergo routine screening for HCC. These patients were followed outside the study protocol for various reasons. The etiology of underlying disease in the two groups was similar, as was the age and gender.

Outcomes analyzed were incidence of HCC and mean time to HCC. During the mean follow-up of 52 months, focal hepatic lesions that proved to be HCC were found in 24 (6.7 percent) of the patients in the screening group. Of the 24 cases, 18 (75 %) were unifocal and six were multifocal. All of the unifocal cases were less than 3 cm. At the time of diagnosis, serum AFP was normal (less than 20 ng/mL) in 11 patients, between 20 and 200 ng/mL in nine patients, and above 200 ng/mL in four patients. At these thresholds, sensitivities for detecting HCC were 46 percent, 38 percent, and 17 percent, respectively. In the control group, HCC was found in 129 (6 %) of the patients over the follow-up period. Only 20 (16 %) of these HCC's were unifocal and 16 percent had tumors that were less than 3 cm. Using serial ultrasonography and serum AFP on a population of patients at risk made it possible to detect small tumors in a high percentage of cases (75 percent versus 16 percent).[147] In this study serum AFP had poor sensitivity.

Summary

In this study of European patients with hepatitis C who were followed over time with ultrasound and AFP studies, HCC was detected earlier and was more often resectable when compared to patients who received standard care [Evidence Grade C].

Q3b *What are the sensitivity, specificity, and predictive values of tests that could be used to screen for HCC (especially resectable carcinoma)?*

Results of Literature Search on Performance Characteristics of Screening Tests for HCC

Through the abstract review process we identified 40 articles that could have data on one of our key questions about screening for HCC in patients with chronic hepatitis C. After reviewing these 40 articles, we found 23 studies provided information on the performance characteristics of screening tests.

Characteristics of Studies on Performance Characteristics of Screening Tests for HCC

Most of the studies were performed in cirrhotics, who are thought to be at highest risk of HCC. Evidence Table 25 summarizes the aims and eligibility criteria of this study. The studies are remarkable in that most were conducted in Europe or Asia with one study from Australia[148] and one from the United States.[149] Almost all studies excluded patients with other forms of liver disease such as hemachromatosis, autoimmune hepatitis, sclerosing cholangitis, and hepatitis delta infection. We evaluated studies of patients with hepatitis C infection only, as well as studies that included patients with hepatitis C or hepatitis B or both. We did not, however, include studies that evaluated screening methods only in patients with hepatitis B alone because the pathogenesis of hepatitis B and its association with HCC is believed to be different from that of hepatitis C.

Evidence Table 26 reveals the demographic and clinical characteristics of the study population. In all of the studies, the majority of participants were men, with the mean age ranging between 31 and 66 years. Most had advanced liver disease, the group thought to be at highest risk of HCC. Duration of infection, if reported, was generally over ten years. Genotypes were obtained routinely and varied according to the country in which the study was perfomed.

Quality of Studies on Performance Characteristics of Screening Tests for HCC

The quality of the study design varied widely for these studies and included cohort studies, case-control studies, and case-series. Table 27 shows the overall quality scores for articles pertaining to this question. The overall mean quality score for this group of studies was 63 percent. The median score for the studies was 65 percent with a range of 32 percent to 87 percent. The interquartile ranges were 57 percent and 70 percent. The mean scores for description and statistics were greater than 75 percent. A particular area of weakness of these

studies as a group was bias. Also, few studies reported both the funding source and the type and degree of involvement of the funding agency.

Results of Studies on Performance Characteristics of Screening Tests for HCC

Twenty-four studies met criteria for key question 3b (see Evidence Table 28). These studies were heterogeneous evaluating serologic, urinary, and radiologic studies. Numerous studies evaluated AFP. Two studies evaluated DCP and one study each evaluated Interleukin-2 receptor, tumor necrosis factor, interleukins 10 and 15, cytokeratin 19, MAGE-4, PIVKA-II, des gamma-carboxy prothrombin *les culinaris* AFP, and p53 antibody. One study evaluated urinary transforming growth factor beta. There were fewer studies evaluating radiologic tests than serologic tests, with six studies evaluating hepatic ultrasound and two studies evaluating computerized tomography or magnetic resonance imaging.

Screening with Alpha Fetoprotein in Patients with HCV Alone

As shown in Evidence Table 28, the studies evaluating use of serum AFP to detect HCC used different thresholds for sensitivity, specificity, and predictive values. Studies using AFP alone had variable sensitivities (Figure 2). The data on the following three studies are in patients with hepatitis C. One cohort study of 163 cirrhotics had a sensitivity of 27 percent with a threshold of 20 ng/mL and 4.5 percent with a threshold of 400 ng/mL.[117] By contrast, in another cohort study of Italian hemophiliacs with hepatitis C, the sensitivity of AFP was 100 percent for levels greater than 11 ng/mL and 17 percent if AFP was greater than 400 ng/mL.[150] A diagnostic test design study revealed decreasing sensitivities of 86 percent, 43 percent, and 14 percent as the AFP threshold increased from 20 to 100 to 400 ng/mL in German patients with hepatitis C.[151]

Screening with Alpha Fetoprotein in Patients with HCV or HBV

Seven cohort studies of patients with hepatitis B or C or both revealed varying sensitivities at different AFP thresholds and in different study populations.[106,148,149,153,154,158,163] Figure 2 displays different AFP thresholds versus sensitivity, and Figure 3 shows different AFP thresholds versus specificity. As expected, the sensitivity decreased as the threshold for AFP increased.

A cohort study using a threshold value for AFP of 81 ng/mL reported a sensitivity of 17 percent,[148] compared to sensitivities of 75 percent and 80 percent for a threshold of 10 ng/mL in two other cohort studies.[153,163] In another cohort study, which evaluated different thresholds of AFP, the highest accuracy was with an AFP threshold of 24 ng/mL, resulting in a sensitivity of 41 percent and specificity of 95 percent.[149] A final cohort study by Cottone[106] revealed a sensitivity of 36 percent for an AFP threshold of 50 ng/mL which decreased to zero percent as the AFP threshold increased to 400 ng/mL.

A prospective cohort study by Ishii and colleagues, which compared AFP and protein-induced vitamin K absence (PIVKA-II), demonstrated sensitivities of 61 percent for AFP greater than 20 ng/mL, 45 percent for AFP greater than 40 ng/mL, 41 percent for PIVKA-II greater than 60 mAU/ ml, and 66 percent for AFP greater than 40 ng/mL and PIVKA-II greater than 80

mAU/mL.[154] Specificities for these same cutoffs were 78 percent for AFP greater than 20 ng/mL, 91 percent for PIVKA greater than 60 mAu/mL and 85 percent for a combination of AFP greater then 40 ng/mL and PIVKA-II greater than 80 mAU/mL.[154]

A retrospective cohort study by Trevisani and colleagues determining the prevalence of etiologic factors and clinical manifestations of HCC in patients with and without cirrhosis demonstrated differing sensitivities for AFP levels as determined by the tumor presentation. Sensitivity for solitary and massive HCCs was approximately 50 percent for an AFP threshold of 20 ng/mL, but sensitivity increased to 70 percent for diffuse and multinodular HCC with the same AFP threshold. Increasing the threshold to 400 ng/mL resulted in sensitivities of 14 percent, 38 percent, 38 percent, and 27 percent, respectively, for the different HCC stages.[158]

Three case-control studies evaluated AFP and other serologic and urinary markers for detecting HCC,[152,161 155] and another evaluated the frequency of increased AFP level among Chinese patients with HCC.[159] Sassa et al.[155] showed greater sensitivity for detection of HCC less than 2 cm when using simultaneous measurement of high sensitivity des gamma carboxy prothrombin at greater than 40 mAU/mL and *lens culinaris* agglutinin A-reactive AFP of greater than 10 percent when using AFP alone with a threshold of 200 ng/mL, (54 percent versus 8 percent).[155] Using this combination of tests resulted in a specificity of 98 percent versus100 percent in those with AFP alone. A case control study by Tsai demonstrated increasing sensitivity of AFP from 64 to 77 percent as the threshold decreased from 400 ng/mL to 20 ng/mL.[161]

Another case-control study revealed that urinary transforming growth factor beta-1 levels increased in patients with cirrhosis and HCC compared to those with cirrhosis alone or healthy controls.[152] In addition, the sensitivity of AFP for detecting HCC increased from 48 percent to 55 percent as the threshold for AFP decreased from 400 ng/mL to 100 ng/mL. When urinary TGF-beta 1 was used in combination with AFP, the sensitivity for detecting HCC was 84 percent if the AFP threshold was 100 ng/mL and 80 percent if the AFP threshold was 400 ng/mL.

In the study of Chinese patients with hepatitis B or C, the sensitivity of AFP increased from 54 to 74 percent as the threshold of AFP decreased from 400 ng/mL to 20 ng/mL. The specificity for AFP greater than 20 ng/mL was 100 percent.[159]

In a cross sectional study by Cedrone, different levels of AFP were compared for diagnostic accuracy in detecting HCC in patients with cirrhosis and in all patients.[157] As the AFP threshold value decreased from 200 ng/mL to 10 ng/mL, the sensitivity for detecting HCC increased from 20 to 76 percent in patients with cirrhosis and all patients, while the specificity decreased from 99 to 60 percent in cirrhotics and from 99 to 78 percent in all patients. The threshold yielding the greatest overall accuracy was 83 percent for a threshold of 50 ng/mL in all patients and an accuracy of 71 percent for an AFP threshold of 13 ng/mL in cirrhotics. Positive predictive values varied from 48 to 88 percent in all patients and 65 to 94 percent in cirrhotics at the same thresholds.[157]

A case series of patients with HCC evaluated different thresholds for AFP and found sensitivities of 62, 55, and 43 percent for thresholds of greater than 20 ng/mL, greater than 50 ng/mL, and greater than 400 ng/mL.[156] Interestingly, AFP appeared to be a more sensitive marker of HCC in patients with hepatitis C than in those with other liver conditions.[156]

Other Serologic Markers

Des gamma carboxy prothrombin (DCP) and lens culinaris agglutinin A-reactive AFP In a case-control study of patients with chronic hepatitis, cirrhosis, or HCC, Sassa et al,[155] showed greater sensitivity for detection of HCC less than 2 cm when using simultaneous measurement of high sensitivity DCP at greater than 40 mAU/mL and *lens culinaris* agglutinin A-reactive AFP of greater than 10 percent than when using AFP alone at a threshold of 200 ng/mL (54 percent versus 8 percent).[155] Using high sensitivity DCP at greater than 40 mAU/mL and *lens culinaris* agglutinin A-reactive AFP of greater than 10 percent together resulted in a specificity of 98 versus 100 percent in those with AFP alone.[155] Another study by Nomura of patients with chronic hepatitis C revealed different sensitivities for DCP using conventional DCP (17 percent), overnight DCP (29 percent), and avidin biotin complex DCP (33 percent).[162]

Interleukin-2 receptor In a cohort study of those with hepatitis B or C or both, a soluble interleukin-2 (IL-2) receptor level greater than 850 U/mL was significantly more sensitive than an AFP level greater than 10 ng/mL (sensitivity 99 percent versus 80 percent).[163] The specificity of soluble IL-2 receptor level and AFP at these thresholds were both 95 percent.

Tumor necrosing factor (TNF) alpha receptor, interleukin-10 (IL-10), and interleukin-15 (IL-15) As shown in Evidence Table 28, a prospective cohort study by Kakumu evaluating the use of TNF-alpha receptor and interleukins 10 and 15 to detect HCC found that IL-10 was significantly higher in HCC patients than in asymptomatic carriers and patients with chronic hepatitis. TNF-alpha receptor also was significantly elevated in HCC cases compared with patients with chronic hepatitis.[164] The sensitivity of IL-10 greater than 5 pg/mL was 63 percent, sensitivity of IL-15 greater than 70 pg/mL was 45 percent, and sensitivity of TNF-alpha receptor could not be calculated.as the data was not presented in an abstractable format.[164]

Cytokeratin 19 (CK-19) In a case-control study in Japan, cytokeratin 19 (CK-19) fragments in the serum of patients with HCC were significantly elevated compared with patients with chronic hepatitis C and those with liver cirrhosis.[165] CK-19 was elevated in 12.3 percent of HCC patients with normal AFP. The sensitivity of CK-19 fragment levels greater than 2.6 ng/mL for the detection of HCC was 47 percent with a specificity of 95 percent.[165]

MAGE-4 A cross sectional analysis by Tsuzurahra and colleagues study that evaluated use of serum MAGE-4 to detect HCC in patients with hepatitis C reported a sensitivity of 47 percent and specificity of 95 percent for a threshold of 1.04 ng/mL[166] and a sensitivity of 45 percent for a threshold of 2.5 ng/mL.

PIVKA-II Another prospective cohort study by Ishii and colleague in patients with hepatitis B or C or both that compared AFP and PIVKA-II found a sensitivity of 61 percent for AFP greater than 20 ng/mL, 45 percent for AFP greater than 40 ng/mL, 41 percent for PIVKA-II greater than 60 mAU/mL, and 66 percent for AFP greater than 40 ng/mL and PIVKA-II greater than 80 mAU/mL.[154] Specificities for these same cutoffs were 78 percent for AFP greater than 20 ng/mL, 91 percent for PIVKA greater than 60 mAU/mL, and 85 percent for a combination of AFP greater then 40 ng/mL and PIVKA-II greater than 80 mAU/mL.[154]

P53 autoantibodies In a cross-sectional study by Raedle and colleague of patients with hepatitis C, positive p53 autoantibodies had a sensitivity of 43 percent and a specificity of 100 percent.[151] Combination of p53 antibody with AFP greater than 100 ng/mL resulted in a sensitivity of 71 percent and specificity of 99 percent. Decreasing the threshold of AFP to 20

ng/mL with positive p53 antibodies increased sensitivity to 86 percent with a specificity of 86 percent.[151]

Circulating immune complexes In a case control study by Tsai and colleagues,[161] evaluating 3 percent pegcirculating immune complexes (CIC), they reported a sensitivity of 65 percent and a specificity of 100 percent in cirrhotics with hepatitis B or C. When combined with AFP at a threshold of 120 ng/mL, the sensitivity increased to 84 percent and the specificity remained 100 percent. When the AFP threshold was increased to 400 ng/mL, the sensitivity remained relatively unchanged at 83 percent, and the specificity remained 100 percent.

Urinary Transforming Growth Factor (TGF)-Beta 1

In a case-control study in Taiwan, the sensitivity of urinary TGF-beta 1 for detecting HCC was 53 percent using a threshold of greater than 50 micrograms per gram of creatinine. When urinary TGF-beta 1 was used in combination with AFP, the sensitivity for detecting HCC was 84 percent if the AFP threshold was 100 ng/mL and 80 percent if the AFP threshold was 400 ng/mL.[152]

Ultrasound

A study evaluating use of computerized tomography (CT) or ultrasonography[167] to detect HCC provided limited data on the utility of screening tests as the study was designed primarily to evaluate the incidence of HCC in patients with hepatitis C.[167] However, the study data indicated a specificity of 96 percent for the combination of the tests.

Studies of ultrasonography with patients having hepatitis B or C or both revealed heterogeneous results. An Australian study by Larcos et al[148] evaluated the utility of sonographic screening for HCC by reviewing 647 ultrasounds in patients with chronic hepatitis or cirrhosis. According to the study, liver masses were detected by sonography in 25 patients (11 percent); however, only six ultimately had HCC. In an Italian study by Izzo et al.[153], evaluating the outcomes of patients with chronic hepatitis screened for HCC with ultrasound, the sensitivity of ultrasonography was 87 percent at detecting tumors at baseline or in follow-up. A prospective cohort study of cirrhotic patients with HCV or HBV revealed a sensitivity of 49 percent for ultrasound.[168] Two other cohort studies evaluating ultrasonography of the liver demonstrated varying sensitivities of 66 percent[163] and 100 percent with 98 percent specificity.[149]

Finally, a study of 154 consecutive patients with HCC in Belgium demonstrated that ultrasonography had a sensitivity of 51 percent.[156] In this study, the most common cause for error on interpretation of ultrasound was between regenerative nodules and HCC.[156]

Computerized Tomography and Magnetic Resonance Imaging

The study evaluating use of CT or ultrasonography[167] in patients with hepatitis C to detect HCC provided limited data on the utility of screening tests as the study was designed primarily to evaluate the incidence of HCC in patients with hepatitis C. However, the study data indicated a specificity of 96 percent for the combination of the tests. A study by Colombo reported a sensitivity of 93 percent for the combination of ultrasound and CT in cirrhosis patients.[168] Another study in patients with either hepatitis B or C or both reported a sensitivity of 100 percent for computerized tomography or magnetic resonance imaging of the liver.[163]

AFP and Ultrasound

Several studies compared the sensitivities of ultrasound and AFP,[149,156,163,169] but did not use the tests in combination. One study, however, evaluated the sensitivity of AFP greater than 10 ng/mL with ultrasound and demonstrated a sensitivity of 100 percent. There was an increase in sensitivity compared to either test alone: AFP greater than 10 ng/mL, (75 percent) and ultrasound, (87 percent).[153]

Summary of Studies on Performance Characteristics of Screening Tests for HCC

The evidence on the value of AFP in screening for HCC in patients with hepatitis C was based on a moderate number of very heterogeneous studies that have important methodologic limitations. These studies were relatively consistent in demonstrating that the sensitivity of AFP for detecting HCC in patients with hepatitis C increases from about 10 percent to 100 percent as the threshold value decreases from 400 ng/mL to 10 ng/mL, with the corresponding specificity decreasing from about 100 percent to 90 percent [Evidence Grade B].

The evidence on the value of IL-2 receptor, TNF, Interleukins 10 and 15, CK-19, MAGE-4, PIVKA, DCP, *lens culinaris agglitutinin A-reactive AFP* and p53 autoantibody in screening for HCC in patients with hepatitis C were based on one or two studies each, and had important methodologic limitations [Evidence Grade I]. These studies demonstrated that of all the tests, the sensitivity of IL-2 receptor for detecting HCC in patients with hepatitis C was the best at 99 percent; however, future research on other possible tests and combinations with AFP may be useful in determining the ideal screening regimen for HCC.

The evidence on the value of urinary transforming growth factor beta in screening for HCC in patients with hepatitis C was based on one study that had important methodologic limitations. This study indicated that the sensitivity of urinary transforming growth factor beta for detecting HCC in patients with hepatitis C was 84 percent [Evidence Grade I].

The evidence on the value of ultrasound in screening for HCC in patients with hepatitis C was based on a moderate number of very heterogeneous studies that had methodologic limitations. These studies demonstrated the inconsistency of ultrasound for detecting HCC in patients with hepatitis C, as sensitivity varied from about 24 percent to 100 percent depending on the study design and study population, with a generally high specificity of 96 percent [Evidence Grade C].

The evidence on the value of CT or magnetic resonance imaging in screening for HCC in patients with hepatitis B or C was based on two studies that had methodologic limitations. These studies were relatively consistent in demonstrating a high sensitivity and specificity of CT or magnetic resonance imaging for detecting HCC in patients with hepatitis C [Evidence Grade C].

The evidence on the value of AFP and ultrasound in screening for HCC was based on one study that had limitations. This study demonstrated an increase in sensitivity from 87 percent to 100 percent when the tests were used in combination for detecting HCC in patients with hepatitis B or C [Evidence Grade C].

Chapter 4: Conclusions

Key Findings

Question 1b: How well do the results of initial liver biopsy predict outcomes of treatment in patients with chronic hepatitis C, taking into consideration patient characteristics such as viral genotype?

- A moderate number of randomized controlled trials addressed this question.
- These studies varied widely in how they reported on the relation of initial histological findings to the outcomes of treatment.
- The analyses for this question had important limitations including frequent lack of reporting of parameter estimates and confidence intervals.
- The studies that used multivariate analysis were relatively but not entirely consistent in suggesting that the presence of fibrosis on initial liver biopsy may predict a modest decrease in the likelihood of having a sustained virological response to treatment.
- The studies suggested that there is no interaction between pre-treatment liver histology and the effect of different treatment regimens on the rate of sustained virologic response.

Question 1e: How well do biochemical blood tests and serologic measures of fibrosis predict the findings of liver biopsy in patients with chronic hepatitis C?

- Numerous studies evaluated the value of biochemical tests and serologic measures of fibrosis in predicting fibrosis on liver biopsy in chronic hepatitis C.
- These studies had some important limitations and varied widely in published evidence: they covered numerous tests and used a variety of methods for reporting results.
- These studies were relatively consistent in showing that 1) serum liver enzymes have only modest value in predicting fibrosis on liver biopsy, 2) the extracellular matrix tests hyaluronic acid and laminin have modest value in predicting fibrosis on liver biopsy, 3) cytokines have less value than the extracellular matrix tests in predicting fibrosis on liver biopsy, and 4) panels of tests may have the greatest value in predicting the absence of more than minimal fibrosis on liver biopsy and in predicting the presence versus absence of cirrhosis on biopsy.

Question 2a: What is the overall efficacy and safety of current treatment options for chronic hepatitis C in treatment naive patients, including peginterferon plus ribavirin, peginterferon alone, standard interferon plus ribavirin and standard interferon plus amantadine?

Peginterferon Plus Ribavirin

- Two published trials evaluated the efficacy of peginterferon plus ribavirin for the treatment of hepatitis C. The results of an additional large trial have not yet been published.
- The largest of these two trials had a relatively high score in all five categories of study quality, but generalizability was limited by the exclusion of patients with HIV infection, previous interferon treatment, mental illness or other significant co-morbidity (among other exclusions).
- The studies were consistent in showing a significant increase in efficacy with peginterferon plus ribavirin compared with standard interferon plus ribavirin or peginterferon alone.

Peginterferon Alone

- A few randomized controlled trials evaluated the efficacy of peginterferon alone for the treatment of chronic hepatitis C.
- These studies had relatively high study quality scores, but differed significantly in the distribution of patients by race/ethnicity, HCV genotype, and presence of cirrhosis.
- These studies were consistent in showing a large relative increase in virological sustained response and a modest increase in histological response with peginterferon compared with standard interferon.

Standard Interferon plus Ribavirin

- A large number of trials evaluated the efficacy of standard interferon plus ribavirin therapy for the treatment of chronic hepatitis C.
- A previous systematic review published demonstrated an increased efficacy of standard interferon plus ribavirin compared with standard interferon alone in treatment-naive patients.
- The additional studies reviewed were somewhat consistent in showing at least a modest increase in virological sustained response with standard interferon plus ribavirin compared with standard interferon alone.
- The magnitude of the relative treatment effect may depend on the dose and duration of treatment as each study used a different treatment regimen.

Standard Interferon Plus Amantadine

- A moderate number of trials evaluated the efficacy of standard interferon plus amantadine for the treatment of chronic hepatitis C.
- Evidence on the efficacy of standard interferon and amantadine was fairly homogeneous with relatively high study quality scores and some variation in treatment protocols.

- The studies were relatively consistent in showing that standard interferon plus amantadine is not more effective than standard interferon monotherapy and is not more effective than standard interferon plus ribavirin in treatment of naïve patients.

Question 2c: What is the efficacy and safety of current interferon based treatment options (including interferon alone) for chronic hepatitis C in subgroups of patients, especially those defined by the following patient characteristics: age less than 18 years, HCV genotype, presence or absence of cirrhosis, minimal versus decompensated liver disease, concurrent hepatitis B or HIV infection, nonresponse to initial interferon based therapy, and relapse after initial interferon based therapy?

Standard Interferon plus Ribavirin: Relapsers and Nonresponders

- A moderate number of trials evaluated the efficacy of standard interferon plus ribavirin for the treatment of chronic hepatitis C in patients who previously failed to respond to interferon or who relapsed after interferon treatment.
- Evidence on the efficacy of standard interferon plus ribavirin in *nonresponders* is heterogeneous and has methodologic limitations including differences in HCV genotype, gender, and treatment protocols among the studies.
- Efficacy data was stronger for sustained virological response than for clinical outcomes like cirrhosis and hepatitis C specific mortality.
- Previous systematic reviews suggested a small but significant increase in sustained virologic response in *nonresponders* receiving combination therapy with standard interferon plus ribavirin.
- The additional studies reviewed were consistent in showing greater efficacy of combination therapy compared with standard interferon monotherapy in improving ETR in nonresponders; however, this response was not consistently sustained through follow-up.
- Evidence on the efficacy of standard interferon plus ribavirin in relapsers and nonresponders combined was heterogeneous and had methodologic limitations.
- A previous systematic review[66] reported that this type of combination therapy had a greater efficacy than standard interferon monotherapy for relapsers and nonresponders combined.
- The additional studies reviewed also were consistent in demonstrating that longer duration of interferon and ribavirin therapy has a greater efficacy than shorter duration in both interferon relapsers and nonresponders. Furthermore, the evidence was consistent in showing that interferon

relapsers have a better response to therapy than do previous nonresponders.

Standard Interferon Plus Amantadine

- Two studies evaluated the efficacy of standard interferon plus amantadine for treatment of chronic hepatitis C in patients who did not respond to previous interferon treatment.
- These studies were small but one had a high study quality score.
- The studies suggested that amantadine plus standard interferon is not significantly more effective than standard interferon alone.
- Only one small study evaluated the efficacy of standard interferon in combination with ribavirin and amantadine compared to interferon and ribavirin in nonresponders.

Interferon Monotherapy

- A moderate number of studies evaluated the efficacy of standard interferon therapy for the treatment of chronic hepatitis C in selected subgroups of clinical interest.
- The evidence on the efficacy of standard interferon in specific clinical subgroups was heterogeneous and had important limitations.
- Few randomized controlled trials of standard interferon therapy focused on HIV-infected patients, renal patients, hemophiliacs, or intravenous drug users.
- The studies that have been done were consistent in showing that standard interferon monotherapy is relatively ineffective in the retreatment of nonresponders and relapsers.

Question 2d: What are the long-term clinical outcomes of current treatment options for chronic hepatitis C?

Interferon- treated Patients

- The evidence on the effect of interferon-based therapy on long-term outcomes in hepatitis C was hetereogeneous and had important methodologic limitations, including variable lengths of follow-up within and among studies, variable numbers of patients with cirrhosis, different doses and durations of therapy (with this information frequently missing), varying amounts of alcohol consumption, and little description of the population that was not treated.
- These studies nonetheless were somewhat consistent in suggesting that treatment with interferon based therapy decreases the risk of HCC and cirrhosis in complete responders.
- The evidence also suggested that biochemical responders may also have a decreased risk of HCC and decreased progression of liver disease.
- The data were inconsistent regarding the impact of interferon therapy in nonresponders and relapsers compared with each other and with untreated

controls. One long-term randomized trial suggested that all patients treated with interferon, regardless of response, derive long-term benefits; other studies suggested that relapsers but not nonresponders or controls derive long-term benefit from interferon therapy.

Natural History

- The evidence on the natural history of hepatitis C was very heterogeneous and had important methodologic limitations.
- These studies, however, were consistent in suggesting that older age, cirrhosis, hepatitis B co-infection, HIV infection, alcohol use, male gender, and initial fibrosis all predict worse long-term outcomes in hepatitis C.
- These studies were somewhat consistent in showing that HCV genotype does not increase the rate of fibrosis progression in patients with chronic hepatitis C.
- These studies were somewhat consistent in showing that HBV co-infection hastens the progression of liver disease in patients with chronic hepatitis C.
- Studies were also consistent in showing that patients with chronic hepatitis C who have a normal ALT have a lower incidence of HCC at five years.

Question 3a: What is the efficacy of using screening tests for hepatocellular carcinoma to improve clinical outcomes in patients with chronic hepatitis C?

- One prospective cohort study and no randomized controlled trials evaluated the efficacy of screening for HCC in patients with chronic hepatitis C.
- This prospective cohort study had important limitations, especially the fact that it included patients with chronic liver disease— primarily due to hepatitis B or C, but also due to other causes— and thus may not be representative of the development of HCC in patients with hepatitis C.
- This study suggested that HCC was detected earlier and was more often resectable in patients who underwent routine screening with AFP and hepatic ultrasound than in those who had usual care.

Question 3b: What are the sensitivity, specificity, and predictive values of tests that could be used to screen for hepatocellular carcinoma (especially resectable carcinoma) in patients with chronic hepatitis C?

- Numerous trials evaluated the performance characteristics of serum AFP in screening for HCC in patients with chronic hepatitis C.

- These studies had important methodologic limitations and varied widely in study design and patient eligibility criteria.
- These studies were relatively consistent in suggesting that a serum AFP level of greater than 10 ng/ml has a moderate sensitivity of 75 to 80 percent and a specificity of approximately 95 percent in screening for HCC, and that a serum AFP level of greater than 400 ng/mL has a low sensitivity with a specificity of nearly 100 percent.
- Several other serologic and urinary screening tests have been evaluated, usually in no more than one study.
- Few of these studies had a large enough population of patients with chronic hepatitis C to provide reliable estimates of the performance characteristics of the tests.
- The studies on use of soluble Interleukin-2 receptor level and protein induced in vitamin K absence (PIVKA-II) suggested that these tests could be useful in screening for HCC if combined with serum AFP or ultrasonography.
- Few studies evaluated the performance characteristics of ultrasonography in screening patients with hepatitis C.
- These studies had some limitations in that they varied by screening frequency, experience of the ultrasonographer, and extent of liver disease in the screened patients.
- The studies were relatively consistent in demonstrating a high specificity of ultrasonography but variable sensitivity depending on the population screened.
- Combination screening with AFP and ultrasound demonstrated an increase in sensitivity in at least one trial with patients having hepatitis B or C.
- Two studies reported on the performance characteristics of computerized tomography and magnetic resonance imaging.
- These studies were limited in that they were not designed to assess the efficacy of screening, but to evaluate the incidence of HCC.
- The studies were consistent, however, in demonstrating both a high sensitivity and specificity in patients with hepatitis C.

Limitations

Limitations of the Studies on Question 1b (Relation of Initial Liver Biopsy Findings to Outcomes of Treatment)

The analyses in these trials were reported in many different ways. Some studies compared the presence and absence of cirrhosis while others used mean HAI or Knodell scores. The methods of statistical analysis were very heterogeneous across the studies, with few studies using multivariate analysis. Some studies used only univariate analysis or reported results stratified by treatment group or virologic outcome. In addition, most

studies presented results in terms of significance for a p value less than 0.05, but few presented adjusted parameter estimates and confidence intervals. While a p value of less than 0.05 indicates a greater chance of a significant relationship, a nonsignificant p value does not mean zero effect. In addition, none of the studies reported a multivariable analysis that examined the potential interaction between pre-treatment histology and the effects of different treatment regimens.

Another limitation is that many different treatment regimens were evaluated, and there tended to be few trials with each type of statistical analysis. Finally, there may be publication bias. Some authors may have evaluated the relation of initial histology to virologic outcomes, but they may not have reported data that did not show a significant relationship.

Limitations of the Studies on Question 1e (Tests for Predicting Fibrosis on Liver Biopsy)

The analyses in these trials were reported in many different ways. Some studies compared the presence and absence of cirrhosis while others used different staging systems including MHAI stage, HAI, METAVIR, Scheur, Desmet and other systems. None of the studies reported side effects or adverse outcomes after liver biopsy. Also, the methods of statistical analysis were very heterogeneous across the studies, with some studies presenting receiver operating characteristic analysis and other studies presenting test characteristics by predictive values of the test.

Limitations of the Studies on Questions 2a/2c (Treatment of Chronic Hepatitis C)

The reported evidence on the efficacy of different treatment options must be weighed against the information on the risk of adverse effects. This limitation is particularly important because the strongest evidence of efficacy is based on the rate of sustained virological response, which is only an intermediate outcome. Treatment studies often lacked variability in racial composition and gender, with most trials including predominately Caucasians and men. The proportion of patients with cirrhosis varied widely across trials. Most trials excluded women who were breast- feeding or pregnant and patients with HIV infection, a history of injection drug use or alcohol use, mental illness, or other significant co-morbidity. In addition, there was often variability in treatment regimens, particularly in trials with standard interferon and ribavirin. Finally, statistical analysis of these studies varied widely with trial results reported in many different ways.

Limitations of the Studies on Question 2d (Long-term Outcomes of Chronic Hepatitis C)

The studies evaluating long-term outcomes of patients with hepatitis C had varying lengths of follow-up both within the study subjects of any one particular study and between studies. In addition, the studies varied widely in the numbers of patients with cirrhosis, doses and duration of therapy, and amount of alcohol consumption reported. Many of the studies gave little description of the population not treated.

Limitations of the Studies on Question 3a (Efficacy of Screening for HCC in Chronic Hepatitis C)

The one study identified was not a randomized controlled trial and therefore had limited validity because of potential selection bias. Also, this study included patients with all forms of chronic liver disease, who may not be representative of patients with chronic hepatitis C.

Limitations of the Studies on Question 3b (Performance Characteristics of Screening Tests for HCC in Chronic Hepatitis C)

Many of the studies on this question included patients with hepatitis B as well as hepatitis C. The pathophysiology of these diseases and their relation to development of HCC is thought to be different; therefore, results of screening tests may be different in these populations. In addition, the heterogeneity of the studies made it difficult to synthesize results across studies and precluded performance of a quantitative meta-analysis of the studies. Finally, in studies evaluating the performance characteristics of hepatic ultrasound, the experience of the ultrasonographer had the potential to greatly influence the results of the study.

Overall Limitations of the Evidence Report

The potential scope of this systematic review of the literature was enormous because of the vast and highly heterogeneous nature of the literature on management of hepatitis C. The EPC team dealt with this challenge by trying to focus the review on the strongest studies on each of the defined key questions.

The EPC team also limited the literature review to articles published in English, thereby introducing potential publication bias. The exclusion of articles not published in the English language reflects the practical realities of obtaining and reviewing the details of non-English studies within the time frame and budget of the project. In addition, non-English studies are likely to be less relevant to the population of hepatitis C patients in the United States, and the Consensus Development Conference will be making recommendations primarily for the management of chronic hepatitis C in the United States. This limitation will be important to consider for clinicians and other groups who may be interested in extrapolating the findings to other populations.

The methods of evaluating diagnostic tests are complex and vary more than the methods of evaluating treatment questions. As a result, it was difficult to anticipate the information that would and would not be available before reviewing the details of all studies. The studies differed so much that it was difficult to extract and synthesize the information into the traditional table-based format of an evidence report. The evidence tables in this report focus on those key pieces of information that could be extracted from two or more studies.

For many of the studies reviewed, the presentation of data was incomplete or otherwise sub-optimal. In some cases, that left gaps in some of the columns of the evidence tables. In other cases, it led to the exclusion of entire studies because none of the results were presented in an extractable format.

Implications

Question 1b (Relation of Initial Liver Biopsy to Outcomes of Treatment)

As indicated in the causal pathway depicted in Figure 1, the evidence on the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C has implications for the clinical decision about whether to obtain a liver biopsy before deciding on treatment. Clinicians may want to consider the lack of definitive evidence on this question when discussing the pros and cons of a liver biopsy with patients.

Future studies will need to be designed to address this question more directly. Such studies should give attention to the methodologic limitations we encountered in trying to extract meaningful information from the studies performed to date. In particular, randomized controlled trials of treatments for chronic hepatitis C should include plans for evaluating whether initial biopsy findings are independent predictors of the efficacy of treatment (measured in terms of virological and/or histological sustained response or other clinical outcomes) and should consider taking into consideration the potential interaction between histological stage of disease and the effects of each treatment strategy.

Question 1e (Tests for Predicting Fibrosis on Liver Biopsy)

As indicated in the causal pathway depicted in Figure 1, the evidence on the correlation of serologic or biochemical tests with liver histology has implications for the clinical decision about whether to obtain a liver biopsy before deciding on treatment. If an alternative, less invasive test could predict findings of liver biopsy, potential complications of the procedure could be avoided. Clinicians may want to consider the lack of definitive evidence on this question when discussing the pros and cons of serologic tests versus liver biopsy with patients infected with HCV.

Future studies should give attention to the methodologic limitations we encountered in trying to extract meaningful information from the studies performed to date. In particular, the studies should provide enough details about the liver biopsy methods to convince readers of the adequacy of the reference standard. Future studies also should give more attention to the potential value of a panel of tests for predicting fibrosis on liver biopsy.

Questions 2a/c (Treatment of Chronic Hepatitis C)

As indicated in the causal pathway depicted in Figure 1, the evidence on treatment regimens for hepatitis C and the possible virologic and histologic outcomes has significant implications for clinicians. Clinicians may want to consider the evidence on both virologic and histologic outcomes of different treatment regimens when discussing treatment options with patients infected with hepatitis C. For treatment-naive patients, the evidence indicates that peginterferon plus ribavirin is the most efficacious treatment option. For patients who did not respond to previous interferon treatment or who relapsed after treatment, the evidence suggests that there are options for achieving a response.

Future studies will need to further address the questions of the optimal doses and duration of therapies. In addition, randomized controlled trials should include traditionally understudied populations with high rates of hepatitis C, such as blacks, injection drug users, alcoholics, and persons with end stage renal disease, HIV infection, hepatitis B, or mental illness. In particular, randomized controlled trials of treatments for chronic hepatitis C should include subgroup analysis by sex and race/ethnicity, as some studies have suggested different response rates between women and men, and between different racial/ethnic groups. Such studies should give attention to the methodologic limitations we encountered in trying to extract key information from the studies performed to date.

Question 2d (Long-term Outcomes of Chronic Hepatitis C)

As indicated in the causal pathway depicted in Figure 1, the long-term sequelae of hepatitis C are significant, including cirrhosis, HCC, and death. If predictors of these complications can be identified, clinicians may be able to identify patients at higher risk and institute preventive measures, such as abstention from alcohol and increased screening for complications.

Future studies will need to assess the long-term outcomes of current treatment options, particularly studies with standard interferon plus ribavirin, as well as new studies with peginterferon. While some data have suggested that longer treatment is better for improving virologic outcomes, little is known about the long-term outcomes of different treatment durations. Finally, although natural history studies may no longer be practical in the current treatment era, following certain subgroups at high risk for complications—

such as patients co-infected with HIV or HBV, injection drug users, and alcoholics— will be useful in making clinical recommendations regarding follow-up for these patients.

Questions 3a/b (Screening for HCC in Chronic Hepatitis C)

As indicated in the causal pathway depicted in Figure 1, the evidence on the efficacy of screening and on the performance characteristics of screening tests has implications for the clinical decision about whether to screen for HCC in patients with hepatitis C. Clinicians may want to consider the varying sensitivities and specificities of different tests, as well as the costs and potential complications of screening tests, when discussing the pros and cons of screening with patients. Screening strategies are most likely to be successful if they are based on the tests that have been shown to have at least moderate sensitivity and specificity.

Future studies should include randomized controlled trials of screening for HCC carcinoma in patients with chronic hepatitis C. While it may be difficult to conduct randomized controlled trials in patients with hepatitis C, including patients at highest risk for HCC in screening trials will make it more likely for future research to determine definitively the benefits of screening. Such studies should consider the use of a combination of screening tests and should consider examining the relative cost-effectiveness of alternative strategies.

Chapter 5: Future Research

Question 1b (Relation of Initial Liver Biopsy Findings to Outcomes of Treatment)

Future treatment studies need to be designed to appropriately answer the question of whether initial liver biopsy findings are associated with a virologic or histologic response to therapy. These studies should use standard techniques for obtaining adequate liver biopsy samples and standardized reporting of liver biopsy results. The studies also should report the details of both univariate and multivariate analyses of the relation of initial biopsy findings to outcomes, including adjusted and unadjusted parameter estimates of the relationship. Such studies would help to provide better estimates of the independent value of liver biopsy in predicting outcomes of treatment options.

Question 1e (Tests for Predicting Fibrosis on Liver Biopsy)

Future studies need to be designed to address this question more directly. Such studies should give attention to the methodologic limitations we encountered in trying to extract meaningful information from the studies performed to date. In particular, the studies should provide enough details about the liver biopsy methods to convince readers of the adequacy of the reference standard. Future studies also should give more attention to the potential value of a panel of tests for predicting fibrosis on liver biopsy.

Questions 2a/c (Treatment of Chronic Hepatitis C)

Future studies need to be designed to further address the questions of the optimal doses and duration of therapies. In addition, randomized controlled trials should include traditionally understudied populations with high rates of hepatitis C, such as blacks, injection drug users, alcoholics, and persons with renal disease or HIV. In particular, randomized controlled trials of treatments for chronic hepatitis C should include subgroup analysis by sex and race/ethinicity, as some studies have suggested different response rates between women and men and between different racial/ethnic groups. Such studies should give attention to the methodologic limitations we encountered in trying to extract information from the studies performed to date.

Question 2d (Long-term Outcomes of Chronic Hepatitis C)

Future studies will need to assess the long-term outcomes of current treatment options, particularly studies with standard interferon plus ribavirin, as well as new studies with peginterferon. Although some data have suggested that longer treatment is better for improving virologic outcomes, little is known about the long-term outcomes of different treatment

durations. Finally, while natural history studies may no longer be practical in the current treatment era, following certain subgroups at high risk for complications— such as patients co-infected with HIV or hepatitis B, injection drug users, and alcoholics— will be useful in making clinical recommendations regarding follow-up for these patients.

Questions 3a and 3b (Screening for HCC)

Future studies should include randomized controlled trials of screening for HCC in patients with chronic hepatitis C. While it may be difficult to conduct large randomized controlled trials in all patients with hepatitis C, including patients at highest risk for HCC in screening trials will make it more likely for future research to determine definitively the benefits of screening. Future studies should consider the use of a combination of screening tests and should consider examining the relative cost-effectiveness of alternative strategies.

Overall Areas of Future Research

Most studies reviewed provided limited information on the type and degree of involvement of the funding source. Consistent with new reporting guidelines accepted by many major journals, this information should become part of the standard data report in future trials.[170]

To improve the quality of publications on these study questions, standardized methods should be developed and disseminated to investigators. Journals should encourage standardized approaches to presenting data on these questions. For published articles, full copies of protocols should be made available, perhaps on the Web. Detailed descriptions of methods are important because the pressure to shorten manuscripts often is met by reducing the description of study methods.

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Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies with multivariate analyses					
Studies comparing peg-IFN + RBV with IFN alpha 2b + RBV					
Manns, 2001	United States Canada Europe Argentina	1530	ALT >34 for women and >43 for men, detectable HCV in serum, nl Cr, initial liver bx w/ CHC in past year, tx naïve, WBC <13, neutrophil >1.5, Hgb 12 for women and 13 for men, plts >100,000, nl Bili, nl Alb	HIV+, immune suppression, depression, other psychiatric illness, decompensated liver disease, comorbidities: cardiovascular, neurologic or hematologic, no contraception, AFP >50 mg/L, DM	To assess the safety and efficacy of two different regimens of Peg IFN and RBV compared w/ IFN alpha 2b and RBV and identify predictors and response for peg IFN alpha 2b.
Studies comparing IFN + RBV with IFN alone					
Berg, 2000	Germany	185	El ALT, any previous treatment, HCV+, detectable HCV in serum	Psychiatric illness, acute or chronic IDU, HBV+, decompensated liver disease, acute or chronic EtOH, immune suppression, plts <100,000, depression, HIV+, severe concurrent diseases, Hgb <11 g/dL, pregnancy	To examine if 12 wk combination therapy is more effective in improving initial and SVR compared w/ IFN monotherapy in untreated pts. Pts who achieved a virologic response were treated w/ IFN alpha monotherapy for an additional 40 wks and then SVR was evaluated 24 wks after end of tx

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies comparing IFN + RBV with IFN alone					
Mangia, 2001	Italy	192	Detectable HCV in serum, ALT available for 6 mos, initial liver bx	DM, HBV+, decompensated liver disease: ascites, bleeding varices, and encephalopathy, pregnancy, depression, EtOH, HIV+, plts <100,000, autoimmune disorder, significant medical illness, IFN monotherapy, WBC <3500, Hgb <12 for females and <13 for males, other psychiatric illness	To compare the efficacy of a high dose regimen of IFN alpha2b (5 mu tiw) for 12 mos alone or in combination w/ RBV for the tx of naïve pts w/ CHC. Secondary aims were to evaluate the effects of baseline features on the response to therapy and to determine a reliable point in time during tx to predict non response.
McHutchison, 2000	United States	1712			To evaluate racial differences in response to therapy in pts w/ CHC, and potential contributing factors that might account for such differences

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Saracco, 2001	Europe	594	HCV+, detectable HCV in serum, initial liver bx w/i prior 2 yrs, nonresponse to previous therapy, IFN monotherapy, age >18 and <65	Concomitant significant medical illness, IDU, HBV+, decompensated liver disease, relapse after previous therapy: >=1 course of IFN, pregnancy, depression, HIV+, cardiovascular comorbidity: ischemic cardiovascular disease, neurologic comorbidity: seizures, hematologic comorbidity: hemolytic anemia or hemophilia, abnl uric acid, obesity-induced liver disease, nonresponse to previous therapy: IFN and ribavirin combination therapy, other comorbidities: Wilson's disease, hemochromatosis, or autoimmune hepatitis, IFN + RBV, WBC <3000, neutrophil <500, Hgb <10 g/dL, plts <70,000, GI comorbidity, alpha-1antitrypsin deficiency	To assess if higher than standard doses of IFN given w/ RBV for prolonged periods of administration improved the rate of sustained response in previous IFN-alone nonresponders. The study compares the efficacy and safety of 3 mu and five mu of IFN plus 1000 mg daily RBV for either 6 or 12 mos

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies comparing peg-IFN with IFN alpha2b					
Lindsay, 2001	United States Europe Australia	1299	U/S: no mass lesion, detectable HCV in serum, initial liver bx w/i 1 yr of enrollment, AFP w/i nl limits, ALT el >= 1 time w/i 6 mos of enrollment, WBC >4, neutrophil >1.8, Hgb >12 in females and > 13 in males, plts > 130	Hemophilia, breast feeding, illicit drug use, HBV+, HCC, pregnancy, HIV+, active IDU, hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, EtOH, NASH, any antiviral therapy, hemoglobinopathy, other medical conditions that could interfere with participation, any prior tx, autoimmune hepatitis	To evaluate the efficacy of pegIFN alpha 2b compared w/ IFN alpha 2b in tx-naïve pts w/ CHC
Studies comparing peg-IFN with IFN alpha2a					
Zeuzem, 2000	Germany	120	HCV+, age >18 and <70 yrs, presence of fibrosis: CHC on liver bx, initial liver bx w/i 1 yr, el ALT for >=6 mos before tx, WBC >2500, plts >70,000	EtOH >50 g/d of ethanol, IDU w/i previous year, GI comorbidity, immune suppression: organ transplant or autoimmune disorder, psychiatric illness, HIV+, HBV+, cardiovascular comorbidity, pregnancy, neurologic comorbidity, malignancy comorbidity, anaphylactic allergy to IFN, other comorbidities: liver disease from another cause OR renal disease OR rheumatologic disease, other viral infections: systemic bacterial or fungal infection, lactation, IFN + RBV, IFN monotherapy, amantadine, hematologic comorbidity	To compare the efficacy, safety, and health related quality of life of IFN alpha alone or in combination w/ amantadine for tx of CHC.

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies comparing different doeses of IFN					
Ascione, 1998	Europe	80	Positive HCV antibodies, ALT 2x nl for 1 yr, initial liver bx: chronic active liver damage or persistent CHC, age 18-60 yrs	Chronic disease that could affect life expectancy, active IDU, homosexual men, HBV+, HCC, pregnancy or absence of contraceptive use in women of childbearing age, immune suppression, GI comorbidity: Fe, copper, alpha-1-antitrypsin deficiency or previous liver decompensation, Alb <3.0 g/L, esophageal varices F2-F3, decompensated DM, any previous therapy, WBC <3000, plts <100,000, Bili >51 µMol/L, HIV+	To see if doubling the dose of IFN improved long-term response. To evaluate efficacy of the tx regimens in cirrhotic pts
Kumada, 1996	Japan	54	ALT >70 IU/L for 6 mos, initial liver bx determination of CHC, presence of cirrhosis, presence of fibrosis, detectable HCV in serum, positive HCV antibodies	Drug-induced liver disease, Wilson's disease, EtOH liver disease, PBC, autoimmune hepatitis, chronic HBV+	To describe the relationship between the therapeutic effect of IFN in CHC pts and various factors including: dosage, age, gender, disease durration, +/- blood transfusion, pre-tx ALT levels, pre-tx liver histology (HAI score), HCV-RNA concentration, and HCV genotype.

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Payen, 1998	France	247	Abnl ALT for 6 mos, initial liver bx IFN monotherapy: 3 mu IFN, tiw for 6 mos, HCV+, detectable HCV in serum	Adverse reaction to previous therapy: grade 3 or 4 by WHO classification, HBV+, presence of cirrhosis, age <18 yrs, HIV+, Fe deposition in liver, women of childbearing age not using contraceptives, severe associated disease, pregnancy	To compare the efficacy of IFN alpha2b regimens in pts w/ CHC who relapsed after an initial 6 mos IFN tx
Studies comparing IFN + amantidine with IFN alone					
Zeuzem, 2000a	Canada Europe Australia	531	HCV+, detectable HCV in serum: RNA >2000 copies per mL, el ALT on >=2 occasions in previous 6 mos, initial liver bx w/ hepatitis, liver bx findings consistent with CHC, adults	Malignancy, decompensated liver disease, HBV+, immune suppression, depression, other psychiatric illness, HIV+, hepatitis A infection, other comorbidities: seizure, neurologic OR cardiovascular, AFP >25 ng/mL, chronic pulmonary disease, autoimmune disorder, unwillingness to practice contraception, severe retinopathy, IFN monotherapy, neutrophil <1500, plts <90,000, Cr 1.5x UL of nl	To compare the efficacy and safety of peg-IFN alpha-2a administered once per wk w/ the efficacy and safety of IFN alpha-2a tiw for 48 wks.

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of IFN + colchicine					
Angelico, 2000	Italy	65	Age: 18-65, ALT >1.5x nl, Ishak score > 1 or < 5 on initial liver bx, detectable HCV in serum,	HBV+	To determine whether the combination of colcichine and IFN alpha is more effective than IFN alpha alone in treating non-cirrhotic pts w/ CHC
Studies with univariate analyses					
Studies of IFN alone					
Saracco, 1997	Italy	164	HCV+, initial liver bx, ALT abnl x 6 mos before entry	Current or past drug addiction,HBsAg+, presence of cirrhosis, HIV+, liver disease of any other etiology	To assess the effects of prolonged tx w/ different doses of IFN alpha 2b on relapse rate of pts w/ CHC. To determine factors predictive of sustained response
Shiffman, 2000	United States	95	WBC >2500, nl PT, nl Bili, HCV+, detectable HCV in serum, plts >90,000	HIV+, active IDU, HBV+, hepatitis delta infection, EtOH "on a regular basis," immune suppression, other viral infections, any other cause of hepatitis, chronic renal failure, pregnancy	To see if pts w/ nl ALT levels and CHC responded to IFN as well as those w/ el ALT levels and if predictors of sustained response could be applied to them as well.
Villa, 2001	Italy	30	Consecutively seen in clinic, ALT 2x nl for 6 mos, HBV+, HCV+	IFN tx, peg-IFN + RBV tx	To determine the outcome of medium to high doses of IFN therapy in pts w/ HBV-HCV.

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of IFN + RBV					
Di Bisceglie, 2001	United States	124	Initial liver bx w/i 12 mos of rx, IFN monotherapy >=36 mu, detectable HCV in serum, positive HCV antibodies		To see if nonresponders to IFN alone would respond to a combination of IFN/RBV for either 24 or 48 wks
Studies of IFN + RBV					
Shiffman, 2000a	United States	140	ALT, IFN monotherapy, pregnancy, nonresponse to previous therapy: IFN monotherapy	IFN monotherapy: max dose 6 mu IFN alpha-2a, OR max dose 9 mg IFN alphacon, OR max dose 3 mu IFN alpha-2b, any other type of liver disease, IDU, EtOH	To determine whether combination IFN/RBV was effective in tx of IFN monotherapy nonresponders. To determine subgroups who did not respond.
Studies of IFN + amantidine					
Mangia, 2001a	Italy	200	Detectable HCV in serum, initial liver bx, el ALT for 6 mos	EtOH, current IDU, depresson, other psychiatric illness, HBV+, decompensated liver disease, plts < 100,000, HIV+, DM, significant medical illness, WBC < 3,500, immune suppression	To assess the efficacy and safety of IFN+amantadine compared to IFN monotherapy in naïve pts w/ CHC
Studies with stratified analyses					
Studies of different types of IFN					
Villa, 1996 A prospective double blinded,	Italy	60	Age >18 and <65 yrs, ALT >2x UL of		Wilson's disease, autoimmune

Evidence Table 1: Overall summary of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
			nl for >= 6 mos	disorder, alpha-1-antitrypsin deficiency, HIV+, immune suppression: immunosuppressive therapy w/i past 6 mos, decompensated liver disease, presence of cirrhosis: Child's grade B or C, HBV+, EtOHism, plts <100,000, WBC, IFN monotherapy	randomized study comparing IFN beta w/ recombinant IFN and leukocyte-derived IFN alpha. The outcomes measured were histological, biochemical, and virological responses.
Studies comparing peg-IFN with IFN					
Heathcote, 2000	United States Canada	271	ALT, initial liver bx	AFP >100 ng/mL, plts <75,000, WBC <500, IFN monotherapy, presence of any other liver disease, comorbidities: malignancy, GI, neurologic, or cardiovascular, HIV+, depression, psychiatric illness, decompensated liver disease	To compare the efficacy and safety of two doses of peg-IFN alpha-2a, given once wkly, w/ the safety and efficacy of a standard regimen of unmodified IFN alpha-2a in pts w/ HCV and cirrhosis or fibrosis.

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies with multivariate analyses										
Studies comparing peg-IFN + RBV with IFN alpha 2b + RBV										
Manns, 2001	RCT									
		IFN: peg-IFN2b, 1.5 mg/kg, qw, 48 wks	511	43 63		Kno	7.9	S3 29		
		RBV: 800 mg qd, 48 wks							1	68.10
									2,3	28.96
									4,5,6	3.13
		IFN (initial): peg-IFN2b, 1.5 mg/kg, qw, 4 wks	514	44 66		Kno	7.9	S3 30		
		IFN (maintenance): peg-IFN2b, 0.5 mg/kg, qw, 44 wks							1	67.90
		RBV: 1000-1200 mg qd, 48 wks							2,3	29.96
									4,5,6	2.33
		IFN: alpha-2b, 3 mu tiw, 48 wks	505	43				S3 28		
		RBV: 1000-1200 mg qd, 48 wks		67		Kno	7.8			
									1	67.92
									2,3	28.91
									4,5,6	3.17

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies comparing IFN + RBV with IFN alone										
Berg, 2000	RCT									
		IFN: alpha-2a, 6 mu tiw, 12 wks	93	42		HAI	S 1.5		70	
		RBV: 7 mg/kg, bid, 12 wks		57					15.2	
									1a	24.73
									1a/b	1.08
									1b	47.31
									2a	2.15
									2a/c	1.08
									2b	3.23
									3a	18.28
									4	2.15
		IFN: alpha-2a, 6 mu tiw, 12 wks	92	42		HAI	S 1.5		82	
				55					14.7	
									1a	20.65
									1a/b	1.09
									1b	54.35
									2a	2.17
									2a/c	1.09
									2b	1.09
									3a	17.39
									4	2.17

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Mangia, 2001	RCT									
		IFN: alpha-2b, 5 mu tiw, 12 mos	96	49		Sch		A>1 19.8		
				72		Sch		A0,1 80.2	8	
						Sch		S1,2 93.8	1b	53.13
						Sch		S3 6.2	2a	33.33
									3	9.38
									other	4.17
		IFN: alpha-2b, 5 mu tiw, 12 mos	96	46		Sch		A>1 26.0		
		RBV: 1000-1200 mg qd, 12 mos		61		Sch		A0,1 74.0	7	
						Sch		S1,2 89.6	1b	41.67
						Sch		S3 10.4	2a	35.42
									3	17.71
									other	5.21
McHutchison, 2000	RCT									
		IFN (210 pts): alpha-2b, 3 mu tiw, 24 wks	1600	43		HAI	7.1			
				65		Kno	S 1.5		17	
		IFN (461 pts): alpha-2b, 3 mu tiw, 24 wks				Kno		S3 1.1	1	65.06
						Kno		S4 0.2	non- 1	34.94
		IFN (464 pts): alpha-2b, 3 mu tiw, 48 wks								
		IFN (465 pts): alpha-2b, 3 mu tiw, 48 wks								
		RBV (461 pts): 1000/1200 mg qd, 24 wks								
		RBV (464 pts): 1000/1200 mg qd,								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		48 wks								
		IFN (12 pts): alpha-2b, 3 mu tiw, 24 wks IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks IFN (15 pts): alpha-2b, 3 mu tiw, 24 wks RBV (13 pts): 1000/1200 mg qd, 48 wks RBV (15 pts): 1000/1200 mg qd, 24 wks	53	46 68		HAI Kno Kno Kno	7.8 S 1.7	 S3 47.2 S4 11.3	18 1 non-1	 96.23 3.77
		IFN (1 pts): alpha-2b, 3 mu tiw, 24 wks IFN (13 pts): alpha-2b, 3 mu tiw, 24 wks IFN (6 pts): alpha-2b, 3 mu tiw, 48 wks IFN (7 pts): alpha-2b, 3 mu tiw, 48 wks RBV (13 pts): 1000/1200 mg qd, 24 wks RBV (7 pts): 1000/1200 mg qd, 48 wks	27	45 81		Kno Kno	S 1.5	 S4 40.7	21 1 non-1	 59.26 40.74

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (12 pts): alpha-2b, 3 mu tiw, 48 wks	32	45 75		HAI HAI	7.9	40.6	21	
		IFN (5 pts): alpha-2b, 3 mu tiw, 48 wks				Kno Kno	S3	6.2	1 non- 1	78.13 21.88
		IFN (7 pts): alpha-2b, 3 mu tiw, 24 wks				Kno	S4	88		
		IFN (8 pts): alpha-2b, 3 mu tiw, 24 wks								
		RBV (12 pts): 1000/1200 mg qd, 48 wks								
		RBV (8 pts): 1000/1200 mg qd, 24 wks								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Saracco, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 12 mos	139	46	12	ISH	A 2.6			
		RBV: 1000 mg qd, 12 mos		66		ISH	S 6.2			
									1	66.91
									2	16.55
									3	9.35
									4	7.19
		IFN: alpha-2b, 5 mu tiw, 12 mos	162	44	9	ISH	A 2.5			
		RBV: 1000 mg qd, 12 mos		75		ISH	S 6.4			
									1	60.49
									2	19.14
									3	13.58
									4	6.79
		IFN: alpha-2b, 3 mu tiw, 6 mos	142	46	15	ISH	A 2.8			
		RBV: 1000 mg qd, 6 mos		77		ISH	S 6.2			
									1	67.61
									2	14.79
									3	14.08
									4	3.52
		IFN: alpha-2b, 5 mu tiw, 6 mos	151	45	7	ISH	A 2.6			
		RBV: 1000 mg qd, 6 mos		78		ISH	S 6.0			
									1	68.87
									2	13.25
									3	11.26
									4	6.62

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies comparing peg-IFN with IFN alpha-2b										
Lindsay, 2001	RCT									
		IFN: peg-IFN2b, 0.5 ng/kg, qw, 48 wks	315	43.1 59 C: 90.1	3	HAI HAI	A 6.8 S 1.4		18.5 1 2 3 other	 67.30 11.11 16.83 4.76
		IFN: peg-IFN2b, 1.0 ng/kg, qw, 48 wks	297	43.7 63 C: 90.9	3	HAI HAI	A 6.9 S 1.4		20.4 1 2 3 other	 67.00 10.10 17.85 5.05
		IFN: peg-IFN2b, 1.5 ng/kg, qw, 48 wks	304	42.9 63 C: 94.0	4	HAI HAI	A 6.7 S 1.3		19.2 1 2 3 other	 73.36 10.53 13.49 2.63
		IFN: alpha-2b, 3 mu tiw, 48 wks	303	42.6 68 C: 89.1	4	HAI HAI	A 7.1 S 1.4		18.6 1 2 3	 71.62 9.24 17.49

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									other	1.65
	Studies comparing peg-IFN with IFN alpha-2a									
Zeuzem, 2000	RCT									
		Amantadine: 100 mg, Twice a day, 48 wks	60	42.1 62						
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 3 mu, tiw, 24 wks							1 2 3 4	70.00 5.00 21.67 1.67
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 3 mu, tiw, 24 wks	60	41.6 60					1 2 3 4	66.67 5.00 25.00 1.67
	Studies comparing different doeses of IFN									
Ascione, 1998	RCT									
		IFN (initial): alpha-2b, 3 mu tiw, 12 mos	40	53				S3, A2 3 7.5	5.74 1b 2a	62.50 37.50
		IFN (initial): alpha-2b, 6 mu tiw, 12 mos	40	70					5.44	

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									1b	67.50
									2a	32.50
Kumada, 1996	RCT	IFN (initial): natural IFN, 5 mu, bid, 20 wks	27	56.1 56		HAI HAI	10.2	CPH I 22.2	6.7	
		IFN (initial): natural IFN, 5 mu, qd, 2 wks				HAI		CPH II a 63.0	1b 1b+2a	44.44 3.70
		IFN (initial): natural IFN, 5 mu, qw, 12 wks				HAI		CPH II b 14.8	2a 2a+2b	44.44 3.70
		IFN (initial): natural IFN, 5 mu tiw, 4 wks							2b	3.70
		IFN (maintenance): natural IFN, 5 mu, bid, 20 wks								
		IFN (maintenance): natural IFN, 5 mu, qd, 2 wks								
		IFN (maintenance): natural IFN, 5 mu, qw, 12 wks								
		IFN (maintenance): natural IFN, 5 mu tiw, 4 wks								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (initial): natural IFN, 10 mu, bid, 20 wks	27	53.4 67				CPH II b 18.5	6.9	
		IFN (initial): natural IFN, 10 mu, qd, 2 wks				HAI	9.1		1b	77.78
		IFN (initial): natural IFN, 10 mu, qw, 12 wks				HAI		CPH I 25.9	1b+2a	0.00
		IFN (initial): natural IFN, 10 mu, tiw, 4 wks				HAI		CPH II a 55.6	2a	11.11
		IFN (maintenance): natural IFN, 10 mu, bid, 20 wks							2a+2b	0.00
		IFN (maintenance): natural IFN, 10 mu, qd, 2 wks							2b	11.11
		IFN (maintenance): natural IFN, 10 mu, qw, 12 wks								
		IFN (maintenance): natural IFN, 10 mu tiw, 4 wks								

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Payen, 1998	RCT									
		IFN: alpha-2b, 3 mu tiw, 6 mos	75	45.6 92 C: 98.6		HAI	7.2		8.83 1 1a 1b 2 3 other	 5.33 10.67 28.00 13.33 16.00 8.00
		IFN: alpha-2b, 3 mu tiw, 12 mos	91	44.1 71 C: 100		HAI	7.6		9.47 1 1a 1b 2 3 other	 3.30 3.30 29.67 15.38 23.08 5.49
		IFN: alpha-2b, 10 mu tiw, 6 mos	81	42.1 70 C: 100		HAI	8		9.08 1 1a 1b 2 3 other	 2.47 3.70 33.33 9.88 28.40 6.17

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies comparing IFN + amantidine with IFN alone										
Zeuzem, 2000a	RCT									
		IFN (initial): peg-IFN2a, 180 µg, qw, 48 wks	267	40.5 67 C: 86.1, B: 2.24, A: 8.98, O: 2.62		HAI	8.6	A1 65.0 A2 30.0 A3 3.3 S1 88.4 S3 7.1	1a 1b 2 3 4 not specified	29.96 32.96 9.36 25.47 1.87 0.37
		IFN (initial): alpha-2a, 6 mu tiw, 12 wks IFN (maintenance): alpha-2a, 3 mu, tiw, 36 wks	264	41 67 C: 84.8, B: 1.89, A: 9.84, O: 3.40		HAI	3.4	A1 60.0 A2 40.0 A3 0.0 S1 84.8 S3 4.9	1a 1b 2 3 4 not specified	31.44 29.55 12.88 23.86 1.14 1.14

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of IFN + colchicine										
Angelico, 2000	RCT									
		IFN (initial): alpha-2a, 6 mu tiw, 6 mos	34	46 59					6.9	
		IFN (maintenance): alpha-2a, 3 mu, tiw, 6 mos							1b non 1b not specified	61.76 32.35 5.88
		Colcichine (initial): 1 mg, 6x/wk, 3 yrs	31	49 58					7.5	
		IFN (initial): alpha-2a, 6 mu tiw, 6 mos							1b non 1b	64.52 25.81
		IFN (maintenance): alpha-2a, 3 mu, tiw, 6 mos							not specified	9.68

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies with univariate analyses										
Studies of IFN alone										
Saracco, 1997	RCT									
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 3 mu, tiw, 21 mos	54	45.4 61					1b	55.56
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 6 mu, tiw, 21 mos	34	48.5 65					1b	44.12
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 6 mu, tiw, 3 mos	65						1b	161.54
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 6 mu, tiw, 18 mos	11							

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Shiffman, 2000	RCT								
		IFN (initial): alpha-2a, 6 mu, qd, 3 mos		47 47	43				21 68.1
		IFN (initial)1: alpha-2a, 6 mu tiw, 3 mos IFN (maintenance): alpha-2a, 3 mu, tiw, 12 mos		C: 59.5					1 74.47
		IFN (initial): alpha-2a, 6 mu tiw, 6 mos		48 52	43.4				10 62.2
		IFN (maintenance): alpha-2a, 3 mu, tiw, 12 mos		C: 45.8					1 75.00
Villa, 2001	RTnc								
		IFN: 6 mu tiw, 6 mos	14	34 71		HAI HAI	A 1.9 S 11.6		 1a 7.14 1b 78.57 2a 14.29
		IFN: 9 mu tiw, 6 mos	16	33 75		HAI HAI	A 1.7 S 11.9		 1a 31.25 1b 43.75 2a 25.00

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of IFN + RBV										
Di Bisceglie, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	63	43		Sch	A0 20.6		90	
		RBV: 1000-1200 mg qd, 24 wks		70		Sch	A1 30.2			
				C: 96.8		Sch	A2 25.4		1	74.60
						Sch	A3 23.8		2	19.05
									3	6.35
		IFN: alpha-2b, 3 mu tiw, 48 wks	61	46		Sch	A0 18.0		100	
		RBV: 1000-1200 mg qd, 48 wks		57		Sch	A1 21.3			
				C: 98.3		Sch	A2 41.0		1	86.89
						Sch	A3 19.7		2	9.84
									3	3.28

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Shiffman, 2000a	RCT									
		IFN (initial): alpha-2b, 5 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu, tiw, 3 mos	48	44.5 60 C: 50, B: 50	21	Kno	7.3		1	89.58
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu, tiw, 3 mos RBV: 1000-1200 mg, divided dose, twice daily, 9 mos	42	43.6 69 C: 69.0, B: 30.9	19	Kno	7		1	88.10
		IFN: alpha-2b, 5 mu tiw, 6 mos RBV: 1000-1200 mg, divided dose, twice daily, 9 mos	50	42.9 66 C: 64, B: 36	14	Kno	6.4		1	90.00

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of IFN + amantidine									
Mangia, 2001a	RCT								
		IFN (initial): alpha-2a, 6 mu tiw, 12 mos	101	48 70		HAI HAI		S0-3 48.5 S1-3 51.5	7.1
									1 59.41
									2a 25.74
									3 10.89
									4 3.96
		Amantadine (initial): 100 mg, bid, 12 mos	99	46 62		HAI HAI		S0-3 36.4 S1-3 63.6	7.1
		IFN (initial): alpha-2a, 6 mu tiw, 12 mos							1 52.53
									2a 34.34
									3 7.07
									4 6.06
Studies with stratified analyses									
Studies of different types of IFN									
Villa, 1996	RCT								
		IFN (maintenance): alpha-2a, 3 mu, tiw, 6 mos	21	45 71	33			S3, A2 66.7	185
		IFN (maintenance): natural IFN, 3 mu tiw, 6 mos	20	46 70	35			S3, A2 65.0	171
		IFN (maintenance): beta IFN, 3 mu, tiw, 6 mos	19	41 79	16			S3, A2 84.2	153

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)

Evidence Table 2: Characterstics of patients in studies addressing the relation of liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies comparing peg-IFN with IFN										
Heathcote, 2000	RCT									
		IFN: alpha-2a, 3 mu tiw, 48 wks	88	46.9 70 C: 87.5, B: 5.68, A: 3.40, O: 3.40	76	HAI	12.8		104.1 1a 1b 2 3 4 not specified	 31.82 21.59 13.64 30.68 0.00 2.27
		IFN: peg-IFN2a, 90 mg, qw, 48 wks	96	47.2 74 C: 90.6, B: 1.04, A: 2.08, O: 6.25	79	HAI	12.7		104.1 1a 1b 2 3 4 not specified	 28.13 32.29 7.29 27.08 2.08 3.13
		IFN: peg-IFN2a, 180 mg, qw, 48 wks	87	47.1 72 C: 86.2, B: 5.74, A: 2.29, O: 5.74	79	HAI	13.4		123.3 1a 1b 2 3 4 not specified	 37.93 17.24 16.09 22.99 1.15 4.60

Evidence Table 3: Methodologic quality of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies with multivariate analyses							
Studies comparing peg-IFN + RBV with IFN alpha 2b + RBV							
Manns, 2001	100	50	0	80	83	50	63
Studies comparing IFN + RBV with IFN alone							
Berg, 2000	90	0	0	85	83	0	86
Mangia, 2001	80	50	0	60	100	0	58
McHutchison, 2000	25	--	--	40	83	50	49
Saracco, 2001	88	100	0	70	100	0	64
Studies comparing peg-IFN with IFN alpha2b							
Lindsay, 2001	90	100	0	85	100	50	75
Studies comparing peg-IFN with IFN alpha2a							
Zeuzem, 2000	100	100	0	60	100	50	87
Studies comparing different doeses of IFN							
Ascione, 1998	100	0	0	80	100	50	56
Kumada, 1996	90	100	0	75	83	0	70
Payen, 1998	75	100	0	85	83	50	81

Evidence Table 3: Methodologic quality of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies comparing IFN + amantidine with IFN alone							
Zeuzem, 2000a	100	50	0	70	100	100	90
Studies of IFN + colchicine							
Angelico, 2000	75	100	0	85	100	100	87
Studies with univariate analyses							
Studies of IFN alone							
Saracco, 1997	70	100	0	75	83	0	66
Shiffman, 2000	88	50	0	80	100	100	89
Villa, 2001	90	50	0	35	67	100	48
Studies of IFN + RBV							
Di Bisceglie, 2001	75	50	0	85	67	50	76
Shiffman, 2000a	100	100	0	60	83	50	69
Studies of IFN + amantidine							
Mangia, 2001a	88	50	0	85	100	50	91

Evidence Table 3: Methodologic quality of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies with stratified analyses							
Studies of different types of IFN							
Villa, 1996	60	0	0	60	33	50	31
Studies comparing peg-IFN with IFN							
Heathcote, 2000	100	100	0	70	83	50	88

[a] ***Representativeness***: The total maximum for this section was 10 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); appropriateness of the spectrum of disease included in the study sample (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 2 points. This included whether there was an independent, blind comparison of initial liver biopsy to outcomes.

[c] ***Description of Biopsy***: The total maximum score was 2 points. This included description of the technique and size of liver biopsy.

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 6 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Biopsy, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C

Author, Yr	Rx Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Multivariate: Other Significant Independent Variables
Studies comparing peg-IFN + RBV with IFN alpha 2b + RBV						
Manns, 2001	A IFN (maintenance): pegIFN2b, 1.5 mg/kg, once wkly, 48 wks RBV (maintenance): 800 mg qd, 48 wks	SVR	Absence of cirrhosis	NR**	NR	Weight, age, HCV viral load, HCV genotype other than 1b
			Absence of bridging fibrosis or cirrhosis	NR	<.01	
	B IFN (initial): pegIFN2b, 1.5 mg/kg, once wkly, 4 wks IFN (maintenance): pegIFN2b, 0.5 mg/kg, once wkly, 44 wks RBV (maintenance): 1000-1200 mg qd, 48 wks					
	C IFN (maintenance): alpha-2b, 3 mu tiw, 48 wks					
Studies comparing IFN + RBV with IFN alone						
Berg, 2000	A IFN: alpha-2a, 6 mu tiw, 12 wks RBV: 7 mg/kg, bid, 12 wks	SVR	Histologic activity, grade and stage	NR	NR	HCV genotype GGT levels
	B IFN: alpha-2a, 6 mu tiw, 12 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx	Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Multivariate: Other Significant Independent Variables
Mangia, 2001	A	IFN (maintenance): alpha-2b, 5 mu tiw, 12 mos	SVR	Histologic grade	NR[b]	NS	Genotype, IFN-ribavirin tx
	B	IFN (maintenance): alpha-2b, 5 mu tiw, 12 mos		Histologic stage	NR[c]	NS	
		RBV (maintenance): 1000-1200 mg qd, 12 mos		Histologic stage	NR[d]	NS	
McHutchison, 2000	A	IFN (210 pts): alpha-2b, 3 mu tiw, 24 wks	SVR	Degree of fibrosis	NR[**]	NR	IFN-ribavirin tx, gender, genotype, baseline viral load, compliance
		IFN (461 pts): alpha-2b, 3 mu tiw, 24 wks					
		IFN (464 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (465 pts): alpha-2b, 3 mu tiw, 48 wks					
		RBV (461 pts): 1000/1200 mg qd, 24 wks					
		RBV (464 pts): 1000/1200 mg qd, 48 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx	Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Multivariate: Other Significant Independent Variables
	B	IFN (12 pts): alpha-2b, 3 mu tiw, 24 wks					
		IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (15 pts): alpha-2b, 3 mu tiw, 24 wks					
		RBV (13 pts): 1000/1200 mg qd, 48 wks					
		RBV (15 pts): 1000/1200 mg qd, 24 wks					
	C	IFN (1 pts): alpha-2b, 3 mu tiw, 24 wks					
		IFN (13 pts): alpha-2b, 3 mu tiw, 24 wks					
		IFN (6 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (7 pts): alpha-2b, 3 mu tiw, 48 wks					
		RBV (13 pts): 1000/1200 mg qd, 24 wks					
		RBV (7 pts): 1000/1200 mg qd, 48 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx	Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Multivariate: Other Significant Independent Variables
	D	IFN (12 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (5 pts): alpha-2b, 3 mu tiw, 48 wks					
		IFN (7 pts): alpha-2b, 3 mu tiw, 24 wks					
		IFN (8 pts): alpha-2b, 3 mu tiw, 24 wks					
		RBV (12 pts): 1000/1200 mg qd, 48 wks					
		RBV (8 pts): 1000/1200 mg qd, 24 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx	Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Other Significant Independent Variables
Saracco, 2001	A	IFN (maintenance): alpha-2b, 3 mu tiw, 12 mos	SVR	Grade ≥5.2	OR: 1.0 (0.73 - 1.45)	0.8	Age ≤44, genotype 2 or 3, tx with 5 mu IFN-ribavirin for 12 mos
				Stage ≥2.3	OR: 0.93 (0.34 - 2.56)	0.8	
		RBV (maintenance): 1000 mg qd, 12 mos		Cirrhosis	OR: 0.5 (0.14 - 1.77)	0.2	
	B	IFN (maintenance): alpha-2b, 5 mu tiw, 12 mos					
		RBV (maintenance): 1000 mg qd, 12 mos					
	C	IFN (maintenance): alpha-2b, 3 mu tiw, 6 mos					
		RBV (maintenance): 1000 mg qd, 6 mos					
	D	IFN (maintenance): alpha-2b, 5 mu tiw, 6 mos					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Multivariate: Other Significant Independent Variables
Studies comparing peg-IFN with IFN alpha-2b						
Lindsay, 2001	A IFN (initial): pegIFN2b, 0.5 ng/kg, once wkly, 48 wks B IFN (initial): pegIFN2b, 1.0 ng/kg, once wkly, 48 wks C IFN (initial): pegIFN2b, 1.5 ng/kg, once wkly, 48 wks D IFN (initial): alpha-2b, 3 mu tiw, 48 wks	SVR	HAI score	OR 2.2, 95% CI (1.1 - 4.8)	NS	HCV genotype other than 1, HCV RNA $\leq 2x10^6$ copies/mL
Studies comparing peg-IFN with IFN alpha-2a						
Zeuzem, 2000	A Amantadine: 100 mg, Twice a day, 48 wks IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 3 mu tiw, 24 wks B IFN (initial): alpha-2a, 6 mu tiw, 24 wks	SVR	Fibrosis at baseline	NR	NS	HCV genotype

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Multivariate: Other Significant Independent Variables
Studies comparing different doses of IFN						
Ascione, 1998	A IFN: alpha-2b, 3 mu tiw, 12 mos	SBR	Liver histology (chronic hepatitis v. cirrhosis)	NR	NR	
	B IFN: alpha-2b, 6 mu tiw, 12 mos					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx	Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Multivariate: Other Significant Independent Variables
Kumada, 1996	A	IFN (initial): natural IFN, 5 mu, bid, 20 wks	SVR	HAI score	0.0018 [a]	0.98	HCV RNA concentration, genotype non 1b
		IFN (initial): natural IFN, 5 mu, once wkly, 12 wks					
		IFN (initial): natural IFN, 5 mu, qd, 2 wks					
		IFN (initial): natural IFN, 5 mu tiw, 4 wks					
		IFN (maintenance): natural IFN, 5 mu, bid, 20 wks					
		IFN (maintenance): natural IFN, 5 mu, once wkly, 12 wks					
		IFN (maintenance): natural IFN, 5 mu, qd, 2 wks					
		IFN (maintenance): natural IFN, 5 mu tiw, 4 wks					
	B	IFN (initial): natural IFN, 10 mu, bid, 20 wks					
		IFN (initial): natural IFN, 10 mu, once wkly, 12 wks					
		IFN (initial): natural IFN, 10 mu, qd, 2 wks					
		IFN (initial): natural IFN, 10 mu tiw, 4 wks					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx	Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Multivariate: Other Significant Independent Variables
Payen, 1998	A	IFN (maintenance): alpha-2b, 3 mu tiw, 6 mos	SVR	Pre-treatment Knodell index	mean 0.76 95% CI (0.61-0.95)	0.015	High level ALT, low viral load, viral genotype = 3, tx for 12 mos
	B	IFN (maintenance): alpha-2b, 3 mu tiw, 12 mos					
	C	IFN (maintenance): alpha-2b, 10 mu tiw, 6 mos					
Zeuzem, 2000a	A	IFN (initial): pegIFN2a, 180 ug, once wkly, 48 wks	SVR	Absence of cirrhosis or bridging fibrosis	NR	0.03	Tx with peg-IFN alpha 2a, age, smaller body surface, decreased HCV RNA, increased ALT quotient, HCV genotype other than 1
	B	IFN (initial): alpha-2a, 6 mu tiw, 12 wks					
		IFN (maintenance): alpha-2a, 3 mu tiw, 36 wks					
Studies of IFN + colchicine							
Angelico, 2000	A	IFN (initial): alpha-2a, 6 mu tiw, 6 mos	Bio-chemical response [e]	Low stage pre-treatment,	NR	0.036	Colchicine tx
				Low grade pre-treatment	NR	0.49	
		IFN (maintenance): alpha-2a, 3 mu tiw, 6 mos					
	B	Colcichine (initial): 1 mg, 6x/wk, 3 yrs					
		IFN (initial): alpha-2a, 6 mu tiw, 6 mos					

Evidence Table 4: Results of studies addressing the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C (continued)

Author, Yr	Rx Group	Outcome	Histological Variable(s)	Multivariate: Adj. Parameter Estimate Relating to SVR	Multivariate: Adj. p-value	Multivariate: Other Significant Independent Variables
	IFN (maintenance): alpha-2a, 3 mu tiw, 6 mos					

[a] Estimate of Cox Proportional Hazard
[b] Based on analysis of total study population
[c] Based on analysis of Group A
[d] Based on analysis of Group B
[e] Similar results were found for SVR, data not presented
* $P < 0.05$
** Text reported that the statistic was significant but did not report the p-value

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Extracellular matrix					
Casaril, 2000	Italy	183	HCV+	Other viral infections: autoimmune hepatitis, HIV+, HCC, decompensated liver disease, IDU, Fe overload w/i 2y, chronic inflammatory disease, EtOH	To investigate the relationship between serum iron load and fibrosis as measured by liver bx and serum tests.
Di Costanzo, 1996	Italy	68	Abnl ALT for > 3 yr, initial liver bx w/compatible histology, HCV+	Large esophageal varices, other causes of liver disease, any disease that increases collagen metabolism, pulmonary fibrosis, rheumatic disease, decompensated liver disease	To evaluate whether assays for connective tissue polypeptides may be clinically useful in predicting primary response to IFN therapy
Fortunato, 2001	Italy	103	Laboratory-confirmed hepatitis C, initial liver bx	Liver disease of any other etiology, HBV+, alcoholism, IFN, any previous therapy	To determine if a multivariate function based on 6 biochemical serum markers can destinguish chronic hepatitis from cirrhosis

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
	Japan	36	Congenital coagulation disorder,		To determine whether serum
Fukuda, 1998			referred to the Hemophilia Group		fibrosis markers predict liver bx results in hemophiliacs
Fukuzaki, 2000	Japan	78		IFN therapy, other chronic liver disease	To observe changes in HA, serum type IV collagen 7S region, and P-III-P in pts with complete, biochemical, or no response to IFN tx
Gabrielli, 1997	Italy	139	ALT 2x UL of nl for 6 mos, initial liver bx showing CHC, positive HCV antibodies	Comorbidity: autoimmune or renal disease, malignancy comorbidity, IDU, other illicit drug use, EtOH >80 g/d	To correlate serum levels of laminin and type III procollagen w/ histology
	Italy	109	ALT >1.5x UL of nl for 6 mo, HCV+	IFN monotherapy, autoimmune	To assess the usefulness of
Giannini, 2001				disease, any extrahepatic disease, HIV+, HBV+, EtOH	serum P-III-P as a marker of hepatic fibrogenesis in pts w/ CHC
	Not specified	176	HCV+, serum alkaline phosphatase	EtOH >50g/day, HBV+, pulmonary	To determine the diagnostic
Guechot, 1994			2x nl, anti-mitochondrial antibodies titer > 1/100	fibrosis, rheumatic disorders,	value of aminoterminal propeptide of type III procollagen level and hyluronan levels in serum as markers of fibrosis
	France	326	Initial liver bx: findings consistent	Rheumatic disease, pulmonary	To determine the diagnostic
Guechot, 1996			with CHC infection, detectable HCV	fibrosis, other chronic liver disease,	accuracy of HA and type III

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
			in serum, HCV+	HBV+	procollagen amino terminal peptide
	Japan	205	Initial liver bx, detectable HCV in	HCC, HBV+	To use common laboratory data
Ikeda, 2000					
			serum, HCV+		to discriminate between chronic hepatitis and cirrhosis.
	Japan	121	ALT 1.5 UL of nl, detectable HCV in	IFN, any previous therapy, serum	To evaluate the effect of IFN tx
Ishibashi, 1996					
			serum, HCV+	autoimmune markers, presence of cirrhosis, HBV+, EtOH	on serum markers of fibrosis
Jeffers, 1995	United States	86	HCV+, initial liver biopsy, ALT el x 6 mos	Heavy EtOH, HBV+, negative autoantibodies, hepatotoxic drugs, other liver disease	To correlate the level of P-III-P w/ HCV-RNA concentration, ALT and histologic severity of disease
	Japan	98	ALT el for >= 6 mo, initial liver bx	EtOH, autoimmune hepatitis, HIV+,	To determine if MMPs MMP-1,
Kasahara, 1997					
			showing CHC, detectable HCV in serum, positive antibodies		and MMP-2, and tissue inhibitors of MMPs, TIMP-1, and TIMP-2, are associated w/ bx findings.
	Germany				To examine the expression,
Lichtinghagen, 1999					
					concentration and activity of MMP-1, -2, -7 and -9 in liver and serum of pts w/ CHC, HCV cirrhosis and healthy controls. To evaluate those parameters as

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
					markers of hepatic fibroproliferation.
	Germany	80	Initial liver bx	Malignancy: assessed with chest	To assess if levels (or ratios) of
Lichtinghagen, 2000					
				x-rays, abdominal U/S, AFFP, CEA, and CA 19-9	MMP-2 and -9, in relation to their tissue inhibitors, are associated w/ stage of HCV induced liver disease. (Levels were assessed for both circulating and expressed proteins in polymorphonuclear and mononuclear leukocytes.)
Lichtinghagen, 2001	Germany	46			To evaluate the correlation between hepatic mRNA expression of MMP-2, -7, -9, TIMP-1, -2, and -3 w/ disease activity of CHC.
	Spain, Italy	52	Abnl ALT, detectable HCV in serum,	Other viral infections:	To investigate the basal levels of
Lo Iacono, 1998					
			HCV+, age 18-60 yrs	non-organ-specific auto-antibodies, HIV+, decompensated liver disease: "clinically advanced cirrhosis," screened HBV antibodies, IDU, EtOH >80 g/d	circulating adhesion molecules and follow changes w/ IFN therapy.
	United States	486	HCV+, initial liver bx > 1cm length,	EtOH, chronic liver disease of any	To determine whether serum HA
McHutchison, 2000a					

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
	Canada		or 3 portal triads	other etiology	was a reliable predictor of cirrhosis and fibrosis
	Japan	176	Initial liver bx	Antiviral therapy, EtOH	To elucidate the clinical
Murawaki, 1999					usefulness of the serum MMP-2 concentration in chronic viral liver disease.
	Japan	165	Initial liver bx, HCV+, plts, ALT,	Presence of fibrosis, presence of	Compare ROC serum IV-C and plt
Murawaki, 2001			collagen, other serological markers, detectable HCV in serum	cirrhosis, decompensated liver disease, peg-IFN monotherapy, peg-IFN + RBV, EtOH, IFN monotherapy, anti-retroviral therapy for HIV, IFN, IFN + RBV	count for predicting fibrosis stage.
	Japan	169	Abnl ALT, detectable HCV in serum	Antiviral therapy, extrahepatic	To assess the usefulness of
Murawaki, 2001a				illnesses, presence of cirrhosis, EtOH	serum fibrotic markers for diagnosing fibrotic staging and necroinflammatory grading in CHC.
	Japan	49	Informed consent, ALT el for >= 6	Drug-induced liver disease,	1. To evaluate HA as a marker of
Ninomiya, 1998			mo, initial liver bx, detectable HCV in serum, HCV+	autoimmune hepatitis, HBV+, EtOH	fibrosis. 2. To investigate the effect of IFN tx on fibrosis.
	Japan	62	Initial liver bx, CHC w/o any other		To clarify the effect of IFN tx on
Ohashi, 1998					

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
			liver disease		the serum markers of hepatic fibrosis and hepatic histological features.
Plevris, 2000	United Kingdom	221	Initial liver bx	IFN tx	To evaluate serum HA as a marker of liver cirrhosis in pts w/ chronic liver disease
Serejo, 2001	Portugal	117	Detectable HCV in serum	Drug-induced liver disease, immune suppression-induced liver disease, HBV+, alcoholic liver disease	To assess clinical significance of serum P-III-P in assessing its ability to act as a marker for fibrogenins in pts treated w/ alpha IFN.
Ueno, 2001	Japan	52	ALT, initial liver bx, detectable HCV in serum, HCV+	Routine medication use, high levels of antinuclear, antibody or antimitochondrial antibody, HBV+, excessive EtOH	To compare hepatic histological changes w/ serum fibrosis markers before and after IFN tx alpha. To investigate the usefulness of serum fibrosis markers in the long-term followup of pts w/ CHC.
Verbaan, 1997	Sweden	109	Initial liver bx, HCV+	IFN tx	To evaluate how well serum levels of P-III-P, IV-C and IgG correlate w/ histological features
Walsh, 1999	United	38		Wilson's disease, alph-1-antitrypsin,	To evaluate the association of

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
	Kingdom			hemochromatosis, HBV+, excessive EtOH	P-III-P (measured by two commercially available tests) and liver fibrosis
	United	52	Detectable HCV in serum, initial liver	EtOH, HBV+, decompensated liver	To determine the
Walsh, 1999a					
	Kingdom		bx	disease, immune suppression, Wilson's disease, alpha-1-antitrypsin deficiency, hemochromatosis, significant extrahepatic disease	sensitivity/specificity of MMP-2, TIMP-1, TIMP-2 in detecting advanced liver disease (ISHAK >/= F3 and HAI > 6)
	Europe	42	CHC via blood, transfusion, HIV-	HBsAg+, absence of liver	To correlate laminin and IV-C w/
Walsh, 2000					
				autoantibodies, nl caeruloplasmin, alpha-1-antitrypsin deficiency, hemochromatosis, EtOH	liver bx findings
Wong, 1998	United Kingdom	130	Detectable HCV in serum, initial liver bx	EtOH, HBV+, HCC, immune suppression, HIV+, liver disease of any other etiology, primary fibrosis, rheumatic disorders	To show that serum HA is a good marker for fibrosis in CHC pts.
	Japan	35	ALT el for >6 mo, initial liver bx	Any antiviral therapy, IFN + RBV,	To examine the effect of IFN on
Yamada, 1996					
			showing CHC, detectable HCV in serum, HCV+	peg-IFN monotherapy, peg-INF + RBV, inflammatory connective tissue diseases, autoantibodies, presence of cirrhosis, HBV+ habitual EtOH	serum HA levels. To determine the correlation between serial serum levels of HA and liver bx findings.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Yamada, 1998	Japan	36	Detectable HCV in serum, HCV+	Any previous therapy, connective tissue disorder, other viral infections: autoantibodies, HBV+, habitual EtOH	To see if serum P-III-P, IV-C and HA correlated w/ stage of liver fibrosis in pts w/ HCV, and to evaluate the effects of IFN therapy on these numbers
Cytokines/cytokine receptors					
Izzo, 1996	Italy	297	AFP, U/S, detectable HCV in serum for >5 yrs, HCV+	Malignancy, HIV+, immune suppression, HCC, decompensated liver disease, HBV+	To determine whether sIL-2R are el in pts w/ CHC and whether these levels correlate w/ histological severity of hepatic injury
Nutt, 2000	United States	70	ALT, initial liver bx, detectable HCV in serum, positive HCV antibodies	GI comorbidity: other chronic liver diseases, HIV+, HBV+	To compare liver histology of HCV+ w/ nl ALT to HCV+ w/ el ALT
Zylberberg, 1999	France, Belgium	154	Detectable HCV in serum, HCV+	Antiviral or immunomodulatory therapy for >= 6 mo, hemodialysis, HIV+	To investigate the relationship between sTNF-alpha receptors and disease activity w/ fibrosis.
Enzymes					
Anderson, 2000	Canada	133	HCV+, ALT el for >= 6 mo	Liver pathology not available, other chronic liver disease	To evaluate the clinical utility of ALT and AST in CHC pts.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Assy, 2000	Canada	79	HCV+	Other previous or concurrent liver disease, drug-induced hepatitis, hemochromatosis, HIV+, HBV+	To assess the predictive values of age, gender, route of transmission, steatosis, EtOH, and ALT and AST on liver bx findings
Barbaro, 1996	Italy	156	HCV+, detectable HCV in serum	Hypertension, chronic, EtOH, HBV+, pregnancy, metabolic liver disease, autoimmune hepatitis, age <18 yrs, diabetes, CD4 <400, hepatotoxic drugs w/i 6 mo, any previous antiviral therapy, WBC <2500, neutrophil < 1000, Hgb <10, Bili >3 x nl, PT >5 over control, Cr >2 x nl, other viral hepatitis	To evaluate the association between glutathione and HIV status, HCV replication, and liver bx findings.
Choi, 1999	United States	38	Serological markers: ALT and HCV-RNA, HCV+		To determine whether ALT levels and histopathological changes in liver bx specimens correlate w/ HCV disease progression or response to IFN tx.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Enzymes					
Goldstein, 1999	United States	81	Bx w/ >3 portal tracts, AFP, initial liver bx, detectable HCV in serum, positive HCV antibodies	Yolk sac carcinoma, HIV+, HCC, HBV+, EtOH >60 g/d for >5 yrs	To show a relationship between AFP, ALT, inflammation and fibrosis, and hepatocyte MIB-1 scores.
Gordon, 2000	United States	1744	HCV+, detectable HCV in serum, ALT abnl x 6 mos prior to study		To see if pretreatment ALT levels correlate w/ histologic features and whether these values influence response to tx
Haber, 1995	United States	90	HCV+, liver bx slides on file	Difficulty making firm HCV diagnosis	To determine the relationship between serum aminotransferase levels and histological grade in HCV
Healey, 1995	United Kingdom	42	HCV+, Detectable HCV in serum, initial liver bx, >= 3 serial transminases of serum alanine aminotransferase		To determine the correlation between liver histology and serum transaminases in hepatitis C infection
Imbert-Bismut, 2001	France	339	Initial liver bx, detectable HCV in serum, HCV+	Inadequate liver bx, other liver disease, HIV+, HBV+	To assess the predictive value of basic serum biochemical markers for diagnosis of liver fibrosis in pts w/ CHC
Imperiale, 2000	United States	177	ALT measured w/i 4 mo of liver bx, initial liver bx between 1993 and	GI comorbidity: primary biliary cirrhosis or primary sclerosing	To evaluate the AST/ALT ratio in ability to diagnose cirrhosis in

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
			1998, detectable HCV in serum, HCV+	cholangitis, Wilson's disease and alpha-1-antitrypsin, autoimmune suppression as cause of liver disease, HBV+	pts w/ CHC infection.
Jamal, 1999	United States	275	ALT in 4 consecutive determinations either all nl or all el, detectable HCV in serum, HCV+, HCV genotype	IFN monotherapy, hemochromatosis, autoimmune disease, immune suppression, HCC, HBV+ <18 yrs	To describe the clinical and histological features of pts w/ CHC and nl ALT levels.
Kobayashi, 2000	Japan	61	Initial liver bx, IFN monotherapy for 6 mos, positive HCV antibodies		To assess the correlation between serial changes in ALT levels and histological outcome 5 yrs after tx of pts w/ CHC w/ IFN for 6 mos.
	Taiwan	93	ALT >=1.5 x nl for >6 mo, HCV+	Renal dialysis, HIV+, HBV+,	To study the relationship
Luo, 1998				metabolic liver disease, hepatotoxic drugs, homosexuality, IDU, EtOH >60 g/d	between ALT levels, histology, serum HCV-RNA and HCV genotypes in pts w/ CHC.
	United States	44	Adequate size of liver bx, other	HBV+	To evaluate whether ALT level
McCormick, 1996			serological markers: ALT w/i 4 wk of liver bx, initial liver bx, nl serum Fe, negative AMA, nl ceruloplasmin, detectable HCV in serum		or HCV-RNA levels can predict histological measures in pts w/ CHC.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Michielsen, 1997	Belgium	51	ALT el for >6 mo, initial liver bx, detectable HCV in serum, CAH	Pts w/persistently nl AST/ALT levels	To determine if a correlation exists between el AST and/or ALT, and histological disease in pts w/ CHC
Ono, 1999	Japan	435	HCV+	HCC: diffuse, HCC or portal vein invasion	To evaluate the stage of liver fibrosis using routine clinical blood biochemistry tests
Park, 2000	Australia	153	El ALT for >= 6 mo w/i 4 mo of bx, initial liver bx: CHC or cirrhosis, presence of fibrosis, HCV+	Antiviral treatment at time of bx, liver disease w/any other etiology, EtOH >20 g/d currently or w/i 5 yrs	To see if AST/ALT ratio greater than one predicted cirrhosis accurately in pts w/ HCV
Poynard, 1997	France	500	Initial liver bx consistent w/ CHC, HCV+	HBV+, any IFN tx, other liver disease	To assess the predictive value of (1)social and clinical factors (age, gender, infection duration, delay between biologic determination and bx, homosexuality, transmission via blood transfuction, transmission by IDU, body weight, ethnicity) and (2) biologicial factors (AST/ALT, GGT, serum bili, serum albumin, PT, WBC, plts, serum Hgb, serum creatinine) for the presence of histologic activity or fibrosis.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Sheth, 1998	United States	139	Biochemical determinations w/i 4 mo of liver bx, ALT el for 6 mo, HCV+		To eva luate whether the ratio of AST to ALT predicts cirrhosis and fibrosis stage in pts w/ CHC infection
Shima, 2000	Japan	36	CHC on initial liver bx	Detectable HCV in serum after prior tx and 3 yrs following tx, metabolic disease, auto immune he patitis, HBV+, alcohol abuse	To evaluate the relationship between serum total bile acid and liver inflammatio n and fibro sis in IFN treate d pts
Stanley, 1996	United Kingdom	100	HCV+		To examine liver histolog y in pts w/ nl an abnl ALT and chronic HCV infection
Tsushima, 1999	Japan	53	Detectable HCV in serum, HCV+		To eva luate the assoc iation of plasma TGF-B1 w/ liver fibrosis.
Yeo, 2001	United States	60	ALT between nl and 2X nl, positive HCV antibodies		To examine the relationship between HCV-RNA levels and severity of disea se in pts w/ chronic HCV
Viral markers					
Adinolfi, 1998	Italy	36	ALT el for >= 6 mo, detectable HCV in serum, positive HCV antibodies	IFN or im munosup pressive ther apy, malignancy comorbidity, immune suppressio n, presence of cirrhosis, HBV+, excessive alcohol intake	To evaluate the relationship between HCV-RNA levels in serum, liver, and periportal blood mononuclear cells and the degree of liver injury in CH C pts

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Iijima, 2000	Japan	135	>= 5 yrs f/u of liver bx, HCV core protein, initial liver bx, detectable HCV in serum, HCV+	IFN tx, any antiviral therapy, malignancy, HIV+, immune suppression, cirrhosis, HBV+, EtOH >80 g/d, age >60 yrs	To determine if HCV viremia correlates w/ degree of fibrosis
Kao, 1996	Taiwan	94	ALT >62 for >1 yr, initial liver bx, detectable HCV in serum, HCV+	Lamivudine for HBV, anti-retroviral therapy for HIV, IFN, any previous therapy, drug-induced hepatitis, immune suppression, HBV+, IDU, EtOH	To clarify the relationship between serum HCV titer and histological severity
Papatheodoridis, 1997	Greece	112	Detectable HCV in serum	HBV+, HIV+, autoantibodies, alcoholic liver disease, therapy in previous 6 mos	To investigate the significance of IgM anti core antibody associations with HCV genotype and liver disease necroinflammatory action
Puoti, 1999	Italy	59	Signed consent, ALT nl 3 times at 2-mo intervals for >= 6 mo, detectable HCV in serum, HCV+	Abnl ferritin, plts <100,000, any previous therapy, HBV+, EtOH >60 g/d for men and >40 g/d for women	To see if HCV carriers w/ nl ALT levels show a correlation between serum HCV-RNA titers and liver histology which could be used as a non-invasive means to separate healthy carriers from those w/ liver damage.

Evidence Table 5: Overall summary of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Miscellaneous					
Bayati, 1998	United States	200	Initial liver bx	EtOH >60 g/d for >5 yrs	To determine the relation between AFP and liver histology in pts w/ CHC.
Chu, 2001	Taiwan	115	ALT 1.5x nl for >6 mos, U/S w/o evidence of HCC, detectable HCV in serum, positive HCV antibodies	Renal dialysis, exposure to hepatotoxic medications, metabolic liver disease, HCC, decompensated liver disease, HBV+, IDU, EtOH >60 g/d	To assess the prevalence of el AFP in pts w/ CHC and to evaluate the clinical, virologic and histopathological significance.

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Extracellular matrix									
Casaril, 2000	CC								
		A: CHC Pts	102	42.5 54		Sch			
		B: Healthy subjects w/ nl liver function tests and negative viral studies	81	44.2 58		Sch			
Di Costanzo, 1996	CohP								
		A: Responders to IFN alpha	22	47.1 77	18	HAI HAI	A 9.5 S 2.2		
		B: Nonresponders to IFN alpha	46	50.3 72	41	HAI HAI	A 9.1 S 2.7		
Fortunato, 2001	XS								
		A: Pts w/ chronic HCV infection	54						
		B: Pts w/ cirrhosis from HCV infection	49						
Fukuda, 1998	CohR								
		O: Hemophilia Pts who had liver bx before IFN tx	36	31 94					

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Fukuzaki, 2000										
		A: Complete response: ALT 2x nl range (<40 U/l) during tx and maintained for 24 wks and HCV RNA- at 42 wks post tx	23	46 39		HAI			78 1b/2a 2b	 39.13 56.52
		B: Biochemical response: ALT 2x nl range (<40 U/l) during tx and maintained for 24 wks and HCV RNA+ at 42 wks post tx	9	53 78					75 1b/2a 2b	 55.56 44.44
		C: No response	46	53 37					105 1b/2a 2b	 91.30 6.52
Gabrielli, 1997										
		A: Pts w/ chronic HCV infection	99	50 64		Sch				
		B: Healthy controls	40							
Giannini, 2001	CS									
		O: Pts w/ chronic HCV infection	109	44 74		HAI/Tri HAI/Tri	S 0.9 A 6.5			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Guechot, 1994	CC								
		A: Pts in cohort of ursodiol for PBC trial	78	9					
		B: Pts in trial of alpha-IFN for viral hepatitis C treatment	58	71					
		C: Healthy controls	40	25					
Guechot, 1996	XS								
		O: HCV+ pts	326	43.6	16	HAI		A0 13.5	
				55		HAI		A1 52.8	
						HAI		A3 17.5	
						HAI		A4 16.2	
Ikeda, 2000	CS								
		O: 205 consecutive Pts w/ CHC	205	56					
				55					
Ishibashi, 1996	CohP								
		A: Complete responders to IFN tx	49						
		B: Relapsers after IFN tx	36						
		C: Nonresponders to IFN tx	36						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Jeffers, 1995	XS								
		A: Pts w/ mild CAH	34			HAI			114
		B: Pts w/ moderate-severe CAH	25						169
		C: Pts w/ cirrhosis	27						160

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Kasahara, 1997	CohP									
		A: IFN tx, sustained response	26	52.2 54		HAI	8.8			
									1b	53.85
									2a	34.62
									2b	3.85
									not specified	0.00
		B: IFN tx, transient response	21	51.7 62		HAI	8.2			
									1b	90.48
									2a	0.00
									2b	4.76
									not specified	9.52
		C: IFN tx, no response	51	55.3 43		HAI	9.2			
									1b	92.16
									2a	5.88
									2b	1.96
									not specified	0.00

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Lichtinghagen, 1999	CS								
		A: Pts w/ CHC presenting to OP clinic				MHAI			
		B: Nl serum and plasma from healthy blood donors							
		C: Livers explanted, but unable to transplant							
		D: Cirrhotic liver from transplant pts							
Lichtinghagen, 2000	CohR								
		A: Healthy controls	20			MHAI			
		B: HCV+ Pts w/ chronic hepatitis	40						
		C: HCV+ Pts w/ cirrhosis	20						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Lichtinghagen, 2001	CS								
		A: Pts w/ CHC	29			MHAI			
		B: Pts w/ CHC and cirrhosis	7						
		C: Nl controls	10						
Lo Iacono, 1998									
		O: CHC virus Pts w/ recurring IFN tx	52	40.8 63		HAI Sch	A 4.4 S 1.6		1b 73.08 non-1b 26.92
McHutchison, 2000a	CohR								
		O: Pts w/ CHC enrolled in a tx study for CHC	486	73				A0 22.2 A1 49.2 A3 12.5 A4 16.0	132

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Murawaki, 1999	CC								
		A: Pts w/ minimal chronic hepatitis.	24	49 83		HAI			
		B: Pts w/ mild chronic hepatitis.	21	51 62					
		C: Pts w/ moderate chronic hepatitis.	17	49 53					
		D: Pts w/ liver cirrhosis	35	58 74					
		E: Pts w/ hepatocellular carinoma.	55	65 69					
		F: Control Pts w/ no liver disease.	24	46 58					
Murawaki, 2001	CS								
		O: Pts HCV+ w/liver bx (fibrosis < F4)	165	53 67		Met/Des Met/Des		S0 9.0 S1 78.0	
						Met/Des Met/Des		S2 40.0 S3 38.0	
Murawaki, 2001a	CohP								
		O: Pts w/ chronic HCV w/o cirrhosis	169	53 66		Des			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Ninomiya, 1998	CohP									
		A: IFN tx, complete response	16	44.9		HAI	A 3.0			
				56		HAI	S 10.8			
		B: IFN tx, partial response	25	42.3		HAI	A 3.2			
				64		HAI	S 9.5			
		C: IFN tx, no response	8	52.6		HAI	A 3.5			
				75		HAI	S 10.9			
Ohashi, 1998	CohP									
		A: Pts who completely responded to IFN.	27	48.8 56		HAI				
									1a	0.00
									1b	25.93
									2a	25.93
									2b	11.11
									mixed	7.41
									not specified	11.11
		B: Pts who did not respond to IFN.	35	54.2 66						
									1a	0.00
									1b	57.14
									2a	8.57
									2b	5.71
									mixed	0.00
									not specified	2.86

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Plevris, 2000	CohP	A: Pts w/ liver disease caused by HCV infection B: Pts w/ liver disease caused by alcohol C: Pts w/ autoimmune liver disease D: Pts w/ primary bilary cirrhosis E: Pts w/ cryptogenic liver disease	69			HAI			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Serejo, 2001	CohP									
		A: Pts who were sustained responders.	44	35.9 64		HAI	A 7.5	A0-A1 50.0 A2 50.0 A3 0.0	1 mixed other	38.64 13.64 20.45
		B: Pts who were relapsers.	35	39.9 51		HAI	A 6.9	A0-A1 65.7 A2 34.3 A3 0.0	1 mixed other	40.00 25.71 17.14
		C: Pts who were nonresponders.	38 68	45.5		HAI	A 11.1	A0-A1 34.2 A2 28.9 A3 36.8	1 mixed other	42.11 7.89 23.68

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Ueno, 2001	CohP								
		A: Complete responders w/ bx done	12	47		Met	A 1.6		71
		<2 yrs after tx.		50		Met	S 1.4		
		B: Nonresponders w/ bx done <2	24	48		Met	A 2.0		77
		yrs after tx		71		Met	S 1.1		
		C: Complete responders w/ bx done	10	51		Met	A 2.5		71
		>2 yrs after tx		60		Met	S 1.1		
		D: Nonresponders w/ bx done >	6	51		Met	A 1.5		94
		2 yrs after tx		67		Met	S 1.3		
Verbaan, 1997	CohR								
		O: Pts w/ CHC infection	109	46		HAI			
				66					
Walsh, 1999									
		A: Pts w/ CHC infection	33			MHAI			
		B: Healthy controls	5						
Walsh, 1999a	CohP								
		A: CHC w/ liver bx	43			MHAI			
				67					
		B: Healthy controls	19						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Walsh, 2000	XS								
		A: Pts w/ chronic HCV infection	37						
				65					
		B: Healthy controls	5						
				80					
Wong, 1998	CS								
		O: CHC virus Pts	130	37					
				72					
Yamada, 1996	CohP								
		A: Pts who were complete responders to IFN tx.	9			Oth			
		B: Pts who were partial responders to IFN tx.	14						
		C: Pts who were nonresponders to IFN tx.	12						
Yamada, 1998	CohP								
		O: Japanese Pts w/ CHC and hemophilia	36	31 94		Des			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Cytokines/cytokine receptors										
Izzo, 1996	CC									
		A: Pts w/ chronic HCV infection	123	53.9						
				67						
		B: Healthy HBV and HCV- controls	174							
Nutt, 2000	CS									
		A: HCV+ consecutive Pts w/ liver	35	44		HAI	A 4			
		bx and nl ALT on >/= 2 occasions		80						
		B: HCV+ consecutive Pts w/ liver bx	35	46		HAI	A 7			
		and el ALT		91						
Zylberberg, 1999	CC									
		A: Pts w/ CHC	60	48						
				68						
									1	60.00
									2	6.67
									3	20.00
									Other	13.33
		B: Pts w/ chronic HBV	34	41						
				76						
		C: Healthy control Pts								

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Enzymes									
Anderson, 2000	CohR								
		O:	133	45.6					
				70					
Assy, 2000	CohR								
		O: Pts w/ chronic HCV infection	79	43.5		Des	S 1.5		
			59			HAI	A 3.5		
Barbaro, 1996	CC								
		A: Pts+ for HIV and HCV infection	55	17		HAI		S0 3.6	
				82		HAI		S1 3.6	
						HAI		S2 47.3	
						HAI		S3 38.2	
						HAI		S4 7.3	
		B: HCV+ pts	50	30		HAI		S0 4.0	
				94		HAI		S1 6.0	
						HAI		S2 42.0	
						HAI		S3 42.0	
						HAI		S4 6.0	
		C: Healthy controls	51	30					
				69					
Choi, 1999	CS								
		O: Pts w/ CHC infection	38	44		Oth			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
				39					
Goldstein, 1999	XS								
		O: CHC Pts given AFP, ALT testing, and liver bx	81						
Gordon, 2000	CohP								
		A: ALT <1.3 x nl in pts w/ HCV	105	40.9		MHAI			
		B: ALT >1.3 x nl in pts w/ HCV	1639	42.9					
Haber, 1995	CS								
		O: Pts w/ serologically confirmed HCV	90	40.9 69		HAI			14.5
Healey, 1995	CohR								
		A: HCV+ normal AST	19	38.9 42		HAI			
		B: HCV+ abnormal AST	23	35.7 61					

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Imbert-Bismut, 2001	XS								
		A: CHC Pts tested in first yr	205	47		Met		A0 25.4	108
		period		53				A1 41.5 A2 30.7 A3 2.4 S0 17.6 S1 44.4 S2 19.5 S3 8.8 S4 9.8	
		B: CHC Pts tested in second yr, as	134	48				A0 12.7	122
		confirmatory group		84				A1 59.7 A2 24.6 A3 3.0 S0 14.9 S1 40.3 S2 20.9 S3 7.5 S4 16.4	
Imperiale, 2000	CohR								
		O: A cohort of Pts w/ HCV.	177	42.3		Oth			
				36					

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Jamal, 1999	CC									
		A: HCV Pts w/ nl ALT levels.	75	44		MHAI	S 1.4			
				60					21	
				C: 46.6, O: 53.3						
		B: HCV Pts w/ abnl ALT levels.	200	44						
				58					20	
				C: 42, O: 58						
Kobayashi, 2000	CohR									
		O: consecutive Pts treated w/	61	47		MHAI			96	
		alpha-IFN for 6 mos w/ f/u of 5 yrs		77						
									1b	86.89
									other	13.11
Luo, 1998										
		O: 93 Pts w/ CHC.	93	53		Oth	A 1.3			
				72			A 2.3			
							A 2.6		1b	38.71
								S1-S2 39.8	2a	13.98
								S3 47.3	2b	11.83
								S4 12.9	mixed	3.23
						HAI	S 1.5		not specified	3.23

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
McCormick, 1996	CohR	O: Pts w/ CHC who were either treated or untreated and were biopsied.	44	77		HAI			
Michielsen, 1997	CS	O: CHC Pts	51	47 53		HAI/Oth			
Ono, 1999	XS	O: Pts w/ chronic HCV infection	435	58 73		Des			
Park, 2000	CohR	O: Pts w/ CHC	153	46.5 64		Sch			20
Poynard, 1997	XS	O: Pts w/ chronic HCV infection	500	49.1 58 C: 97.2, O: 0.8		Met			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Sheth, 1998	CohR									
		A: Ratio of AST to ALT >/= 1 in Pts w/ CHC				Oth				
		B: Ratio of AST to ALT </= 1 in Pts w/ CHC								
Shima, 2000	CohP									
		O: Pts w/ chronic HCV infections w/ sustained response to IFN tx	36	56		HAI		<10 77.8		
				67		HAI		>11 22.2		
Stanley, 1996	CS									
		A: Pts w/ chronic HCV infection and nl ALT	15	38.9		Oth				
									1a	20.00
									3a	13.33
		B: Pts w/ chronic HCV infection and el ALT	85	38.2						
									1a	29.41
									3a	29.41
Tsushima, 1999	CohR									
		A: Pts receiving IFN tx.	43	51.8 74		Oth				
		B: Pts not receiving IFN tx.	10	57.6 80						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Yeo, 2001	CS									
		O: Pts w/ chronic HCV infection	60			HAI				
				47 C: 80, B: 20						
									1a	43.33
									1b	31.67
									2a/b	8.33
									unknown	18.33
Viral markers										
Adinolfi, 1998	XS									
		O: HCV+ Pts undergoing liver bx	36	53	25	HAI		A1 25.0		
		and HCV-RNA levels		64		HAI		A2 33.3		
						HAI		A3 16.7	1b	52.78
									2a/c	33.33
									3a	5.56
									4	2.78
									mixed	5.56
Iijima, 2000	CS									
		O: CHC Pts not receiving antiviral	135	49.5		HAI/Des				
		therapy		70						

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Kao, 1996	XS									
		A: Pts w/ chronic persistent	34	43		Oth			131	
		hepatitis		59					1b	64.71
		B: Pts w/ CAH and/or liver cirrhosis	30	51					162	
				67					1b	66.67
		C: Pts w/ HCC	30	65					74	
				73					1b	80.00
Papatheodoridis, 1997										
		O: Pts w/ chronic HCV	112	43.7		HAI				
				69						
									1a	7.14
									1b	24.11
									2a	5.36
									3a	18.75
									4a	2.68
Puoti, 1999	CohP									
		O: Anti-HCV+ Pts w/ persistently nl	59	47.5		HAI	A 0.8			
		ALT		34		HAI	S 4.0			

Evidence Table 6: Characteristics of patients in studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Miscellaneous										
Bayati, 1998	CS									
		A: Pts w/ a nl AFP level of <10.	125	52.5	46	Des				
				56					22.5	
		B: Pts w/ a high AFP level of >/= 10.	75	57.7	68					
				48					26.4	
Chu, 2001	XS									
		A: Chronic HCV Pts w/ el AFP	33	57 36		HAI/Sch				
									1b	72.73
									non-1b	21.21
		B: Chronic HCV Pts w/ nl AFP	82	49 29						
									1b	45.12
									non-1b	43.90

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Extracellular matrix							
Casaril, 2000	70	50	0	0	100	0	44
Di Costanzo, 1996	60	100	50	75	100	50	77
Fortunato, 2001	50	100	100	50	100	50	80
Fukuda, 1998	50	50	0	100	25	0	45
Fukuzaki, 2000	50	0	0	0	67	0	29
Gabrielli, 1997	60	100	100	50	100	50	82
Giannini, 2001	70	100	100	50	100	0	84
Guechot, 1994	40	0	50	33	100	0	45
Guechot, 1996	60	50	50	50	67	0	55
Ikeda, 2000	90	0	50	100	50	0	58
Ishibashi, 1996	50	0	50	50	100	0	50
Jeffers, 1995	70	100	0	100	75	0	69
Kasahara, 1997	70	100	50	25	67	0	62
Lichtinghagen, 1999	20	0	0	0	33	0	11
Lichtinghagen, 2000	30	100	0	33	100	50	53

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Lichtinghagen, 2001	30	100	0	50	100	50	56
Lo Iacono, 1998	80	100	50	56	67	50	71
McHutchison, 2000a	100	50	50	50	100	0	70
Murawaki, 1999	50	50	0	50	100	50	50
Murawaki, 2001	50	100	50	50	100	50	70
Murawaki, 2001a	50	100	50	0	100	50	60
Ninomiya, 1998	60	50	0	25	67	50	40
Ohashi, 1998	80	50	0	50	100	0	56
Plevris, 2000	30	100	100	50	100	0	76
Serejo, 2001	50	100	0	50	100	0	60
Ueno, 2001	80	100	100	25	67	50	74
Verbaan, 1997	90	100	100	83	67	50	88
Walsh, 1999	50	50	0	67	100	50	53
Walsh, 1999a	50	100	0	50	100	0	60
Walsh, 2000	50	50	0	50	100	0	50
Wong, 1998	80	50	0	100	100	0	66
Yamada, 1996	60	100	0	50	100	0	62

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Yamada, 1998	60	50	50	50	100	0	62
Cytokines/cytokine receptors							
Izzo, 1996	80	0	50	25	67	50	44
Nutt, 2000	60	100	0	100	75	0	67
Zylberberg, 1999	60	100	0	25	67	0	50
Enzymes							
Anderson, 2000	70	0	0	0	100	50	34
Assy, 2000	70	100	0	50	100	50	64
Barbaro, 1996	60	100	100	25	100	0	77
Choi, 1999	40	50	0	50	75	0	43
Goldstein, 1999	60	100	50	50	100	0	72
Gordon, 2000	83	50	0	50	100	0	57
Haber, 1995	100	100	0	100	100	50	80
Healey, 1995	60	100	50	25	17	0	50
Imbert-Bismut, 2001	90	100	50	50	100	50	78
Imperiale, 2000	75	50	0	50	100	0	55

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Jamal, 1999	75	100	0	50	100	0	65
Kobayashi, 2000	75	100	50	50	100	0	75
Luo, 1998	60	100	100	50	100	0	82
McCormick, 1996	50	50	0	50	75	0	45
Michielsen, 1997	70	100	0	50	100	0	64
Ono, 1999	90	100	50	50	100	0	78
Park, 2000	50	50	0	50	100	0	50
Poynard, 1997	50	100	0	50	100	50	60
Sheth, 1998	80	50	0	50	100	0	56
Shima, 2000	60	100	0	50	100	0	62
Stanley, 1996	88	100	50	50	100	0	78
Tsushima, 1999	63	100	100	33	100	0	79
Yeo, 2001	70	100	0	67	100	100	67
Viral markers							
Adinolfi, 1998	60	0	0	50	50	50	32
Iijima, 2000	80	100	0	25	100	50	61

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Kao, 1996	80	50	0	50	100	50	56
Papatheodoridis, 1997	88	100	0	50	100	0	68
Puoti, 1999	70	100	50	50	100	0	74
Miscellaneous							
Bayati, 1998	63	50	0	50	75	0	48
Chu, 2001	90	100	100	50	100	50	88

Evidence Table 7: Methodologic quality of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 10 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); appropriateness of the spectrum of disease included in the study sample (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 2 points. This included whether there was an independent, blind comparison with a reference standard.

[c] ***Description of Biopsy***: The total maximum score was 2 points. This included description of the technique and size of liver biopsy.

[d] ***Outcomes and Followup:*** The total maximum score was 8 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); and proportion of patients who withdrew from the study or were lost to followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 6 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Biopsy, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Extracellular matrix										
Casaril, 2000	A: CHC Pts	102			laminin		Sp: 0.44*			
	B: Healthy subjects w/ nl liver function tests and negative viral studies	81			P-III-P		Sp: 0.30*			
Di Costanzo, 1996	A: Responders to IFN alpha	22	HAI: 2.24		Laminin					
	B: Non-responders to IFN alpha	46	HAI: 2.75		P-III-P					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Fortunato, 2001	A: Pts w/ chronic HCV infection	54			Albumin ALP					
	B: Pts w/ cirrhosis from HCV infection	49			ALT Apo A1 Apo B AST AST/ALT ratio Cholesterol Direct Bili Fibronectin GPX LDII LDL MnSOD PCHE P-III-P Plts PT Total Bili					
Fukuda, 1998	O: Hemophilia Pts who had liver bx before IFN tx	36			HA type IV collagen		n/s: 0.78* n/s: 0.38*			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Fukuzaki, 2000	A: Complete response: ALT twice normal range (<40 IU/l) durring tx and maintained for 24 wks and HCV RNA- at 42 wks post tx	23			HA IV 7s PIIIP					
	B: Biochemical response: ALT twice normal range (<40 IU/l) durring tx and maintained for 24 wks and HCV RNA+ at 42 wks post tx	9								
	C: No response	46								
Gabrielli, 1997	A: Pts w/ chronic HCV infection	99			Laminin P-III-P	1.8 1.0			51.7 34.4	80 20.6
	B: Healthy controls	40								
Giannini, 2001	O: Pts w/ chronic HCV infection	109	Oth: 0.9	Oth: 6.5	P-III-P		Sp: 0.03*			
Guechot, 1994	A: Pts in cohort of ursodiol for PBC trial	78			HA GroupA HA GroupB				0.51 0.55	0.74 0.92
	B: Pts in trial of alpha-interferon for viral hepatitis C treatment	58			PIII NP GroupA PIII NP GroupB				0.62 0.4	0.77 0.66
	C: healthy controls	40								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Guechot, 1996	O: HCV+ pts	326			HA		Pr: 0.58*			
					HA	110		0.92	79.2	89.4
					HA	85		0.86	64.5	91.2
					P-III-P		Pr: 0.34*			
					P-III-P	0.8		0.69	70	63.4
					P-III-P	1.0		0.73	60	74
Ikeda, 2000	O: 205 consecutive Pts w/ CHC	205			gamma globulin	10 x 10^4 / mm^3	n/s: 0.57 [b]			
					gender	10 x 10^4 / mm^3	n/s: -0.21 [b]			
					HA	10 x 10^4 / mm^3	n/s: 0.42 [b]			
					Plts	10 x 10^4 / mm^3	n/s: -0.43 [b]		81.1	89.8
Ishibashi, 1996	A: Complete responders to IFN tx	49	HAI: 1.4	HAI: 6.3	HA		Sp: 0.51*			
					IV-75		Sp: 0.42*			
	B: Relapsers after IFN tx	36	HAI: 1.3	HAI: 6.4	P-III-P		Sp: 0.33*			
	C: Non-responders to IFN tx	36	HAI: 2.1	HAI: 7.7						
Jeffers, 1995	A: Pts w/ mild CAH	34			P-III-P	Abnormal			70	
	B: Pts w/ moderate-severe CAH	25			P-III-P	Abnormal			58	82
	C: Pts w/ cirrhosis	27								
Kasahara, 1997	A: IFN tx, sustained response	26	HAI: 2	HAI: 6.8	MMP-2		Sp: 0.26*			
	B: IFN tx, transient response	21	HAI: 1.7	HAI: 6.5	TIMP-1		Sp: 0.30*			
	C: IFN tx, no response	51	HAI: 2.3	HAI: 7.4						

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Lichtinghagen, 1999	A: Pts w/ CHC presenting to OP clinic B: Nl serum and plasma from healthy blood donors C: Livers explanted, but unable to transplant D: Cirrhotic liver from transplant pts				MMP-1 MMP-2 MMP-7					
Lichtinghagen, 2000	A: Healthy controls B: HCV+ Pts w/ chronic hepatitis C: HCV+ Pts w/ cirrhosis	20 40 20			MMP-2 MMP-9 Ratio of MMP-2:TIMP-1 TIMP-1 TIMP-2		Sp: ns Sp: ns Sp: -0.38 Sp: ns Sp: ns			
Lichtinghagen, 2001	A: Pts w/ CHC B: Pts w/ CHC and cirrhosis C: nl controls	29 7 10			MMP-7 MMP-9 TIMP-1 TIMP-2 TIMP-3 TIMP-4		Sp: 0.53* Sp: 0.39* Sp: 0.46* Sp: 0.34 ns Sp: 0.52*	0.75 0.67 0.76 0.66 0.55 0.72		
Lo Iacono, 1998	O: CHC virus Pts w/ recurring IFN tx	52	Sch: 1.6	HAI: 4.4	P-III-P sICAM-1 sVCAM-1	>10.57 >520 >1280		0.73 0.75 0.96	88.9 63.6 100	51.7 55.9 85.3

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
McHutchison, 2000a	O: Pts w/ CHC enrolled in a tx study for CHC	486	HAI: 1.5	HAI: 2.4	HA		n/s: 0.54*			
					HA	100			76	82
					HA	110			73	83
					HA	60			88	59
					HA	80			83	72
Murawaki, 1999	A: Pts w/ minimal chronic hepatitis.	24			7S collagen	8.5				85
					HA	100				93
	B: Pts w/ mild chronic hepatitis.	21			IV collagen	150				81
	C: Pts w/ moderate chronic hepatitis.	17			MMP-2	700 ng/mL				89
	D: Pts w/ liver cirrhosis	35								
	E: Pts w/ hepatocellular carinoma.	55								
	F: control Pts w/ no liver disease.	24								
Murawaki, 2001	O: Pts HCV + w/liver bx (fibrosis < F4)	165			Plts	14x10^4/mm^3			68	73
					Plts	16x10^4/mm^3			68	71
					Type IV Collagen	110 ng/ml			71	73
					Type IV Collagen	130 ng/ml			66	75

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Murawaki, 2001a	O: Pts w/ chroinc HCV w/o cirrhosis.	169			ALT	80			61	66
					HA	50			75	80
					HA	70			50	79
					IV-C7S	6			70	73
					IV-C7S	6.5			63	73
					MMP-2	550			75	70
					MMP-2	575			68	69
					P-III-NP	0.8			74	52
					P-III-NP	0.9			64	59
					TIMP-1	160			79	56
					TIMP-1	170			82	34
Ninomiya, 1998	A: IFN tx, complete response	16	MHAI: 3	MHAI:	HA after treatment		Sp: 0.56*			
	B: IFN tx, partial response	25	MHAI: 3.2	MHAI: 9.5						
	C: IFN tx, no response	8	MHAI: 3.5	MHAI:	HA before treatment		Sp: 0.61*			
					P-III-P after treatment		Sp: 0.51*			
					P-III-P before treatment		Sp: 0.53*			
					Type IV collagen after treatment		Sp: 0.32*			
					Type IV collagen before treatment		Sp: 0.24			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Ohashi, 1998	A: Pts who completely responded to IFN.	27			HA IV-C		0.49			
	B: Pts who did not respond to IFN.	35			P-III-P		0.53			
Plevris, 2000	A: Pts w/ liver disease caused by HCV infection	69			HA HA	100 200			72 67	95 98
	B: Pts w/ liver disease caused by alcohol				HA	300			47	100
	C: Pts w/ autoimmune liver disease									
	D: Pts w/ primary bilary cirrhosis									
	E: Pts w/ cryptogenic liver disease									
Serejo, 2001	A: Pts who were sustained responders.	44			P-III-P					
	B: Pts who were relapsers.	35								
	C: Pts who were non-responders.	38								
Ueno, 2001	A: Complete responders w/ bx done < 2 years after tx.	12			HA		Sp: 0.29*			
	B: Non-responders w/ bx done < 2 years after tx	24			P-III-P		Sp: 0.33*			
	C: Complete responders w/ bx done more than 2 years after tx	10			type IV collagen		Sp: 0.35*			
	D: Non-responders w/ bx done more than 2 years after tx	6								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Verbaan, 1997	O: Pts w/ CHC infection	109			IgG		Sp: 0.43*			
					P-III-P	1.11	Sp: 0.32*		78	56
					type-IV collagen	250	Sp: 0.43*		87	75
Walsh, 1999	A: Pts w/ CHC infection	33			ALT	155		0.51	71	44
	B: Healthy controls	5			CIS P-III-P	0.8 U/mL		0.76*	50	85.7
					Orion P-III-P	4.2 ng/L		0.67	85	37.5
Walsh, 1999a	A: CHC w/ liver bx	43			ALT			0.59	67	52
	B: Healthy controls	19			MMP-2	860		0.67	69	59
					TIMP-1	500		0.73*	94	57
					TIMP-2	102		0.73*	85	47
Walsh, 2000	A: Pts w/ chronic HCV infection	37			ALT			0.54*		
					Laminin	1.26		0.82*	80	85.3
	B: Healthy controls	5			type IV collagen	148		0.85*	80	73.3
Wong, 1998	O: CHC virus Pts	130			ALT				76	48
					AST				48	39
					HA				86	88
Yamada, 1996	A: Pts who were complete responders to IFN tx.	9	Oth: 2.11		HA		Sp: 0.79*			
					P-III-P		Sp: 0.45*			
	B: Pts who were partial responders to IFN tx.	14	Oth: 1.78		type-IV collagen		Sp: 0.42*			
	C: Pts who were non-responders to IFN tx.	12	Oth: 7.08							

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Yamada, 1998	O: Japanese Pts w/ CHC and hemophilia	36	Desm: 1.9		HA type IV collagen		Sp: 0.78* Sp: 0.38*			
Cytokines/cytokine receptors										
Izzo, 1996	A: Pts w/ chronic HCV infection	123			IL-2R					
	B: Healthy HBV and HCV-controls	174								
Nutt, 2000	A: HCV + consecutive Pts w/ liver bx and nl ALT on >= 2 occasions	35	HAI: 4		ALT					
	B: HCV + consecutive Pts w/ liver bx and elevated ALT	35	HAI: 7							
Zylberberg, 1999	A: Pts w/ CHC B: Pts w/ chronic HBV C: Healthy control Pts	60 34			sTNF-R55 sTNF-R75 TNF-alpha					
Enzymes										
Anderson, 2000	O	133			AST/ALT ratio > 1				31	95
Assy, 2000	O: Pts w/ chronic HCV infection	79	Desm: 1.5	HAI: 3.5	ALT AST		M: 0.51* M: 0.64*			
Barbaro, 1996	A: Pts+ for HIV and HCV infection	55			CD4 plus T-cell count		Pr: 0.02			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
	B: HCV+ pts C: Healthy controls	50 51			Plasma glutathione		Pr: 0.74*			
Choi, 1999	O: Pts w/ CHC infection	38			ALT HCV RNA					
Goldstein, 1999	O: CHC Pts given AFP, ALT testing, and liver bx	81			AFP ALT					
Gordon, 2000	A: ALT < 1.3 x nl in pts w/ HCV B: ALT > 1.3 x nl in pts w/ HCV	105 1639	MHAI: MHAI:	MHAI: MHAI:						
Haber, 1995	O: Pts w/ serologically confirmed HCV	90	HAI: 3.4		ALT/AST					
Healey, 1995	A: HCV+ normal AST B: HCV+ abnormal AST	19 23			AST					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Imbert-Bismut, 2001	A: CHC Pts tested in first year period	205			10 markers in logistic regression, group A			0.86		
	B: CHC Pts tested in second year, as confirmatory group	134			10 markers in logistic regression, group B			0.89		
					6 markers in logistic regression, group A			0.82		
					6 markers in logistic regression, group B			0.85		
Imperiale, 2000	O: A cohort of Pts w/ HCV.	177			AST/ALT	>1			56	90
Jamal, 1999	A: HCV Pts w/ nl ALT levels.	75	MHA I: 1.4		ALT					
	B: HCV Pts w/ abnl ALT levels.	200	MHA I:							
Kobayashi, 2000	O: consecutive Pts treated w/ alpha-IFN for 6 mos w/ f/u of 5 years	61			ALT					
Luo, 1998	O: 93 Pts w/ CHC.	93	Oth: 0.5	Oth: 7.7	ALT					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
					HCV RNA					
McCormick, 1996	O: Pts w/ CHC who were either treated or untreated and were biopsied.	44			ALT HCV titer		Sp: 0.49* Sp: 0.35			
Michielsen, 1997	O: CHC Pts	51			ALT AST		Sp: 0.08 Sp: 0.29*			
Ono, 1999	O: Pts w/ chronic HCV infection	435			ALB Alkaline phosphatase ALT AST GTP LDH Plts PT total Bili WBC	> 4 vs. < 4 1IV 1IV 104 1%				
Park, 2000	O: Pts w/ CHC	153			AST/ALT	1			46.7	95.9

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Poynard, 1997	O: Pts w/ chronic HCV infection	500			Age AST Bili Body weight Creatinine GGT IDU Index: age, Plts Plts PT			0.79		
Sheth, 1998	A: Ratio of AST to ALT >= 1 in Pts w/ CHC B: Ratio of AST to ALT <= 1 in Pts w/ CHC				AST/ALT	> 1				100
Shima, 2000	O: Pts w/ chronic HCV infections w/ sustained response to IFN tx	36	HAI: 2	HAI: 8	Cholinesterase Plts Total bile acid Zinc sulphate turbidity test					
Stanley, 1996	A: Pts w/ chronic HCV infection and nl ALT B: Pts w/ chronic HCV infection and elevated ALT	15 85			ALT	> normal	Sp: ns			
Tsushima, 1999	A: Pts receiving IFN tx. B: Pts not receiving IFN tx.	43 10	Oth: 1 Oth: 2		ALT/AST					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Yeo, 2001	O: Pts w/ chronic HCV infection	60			ALT HCV-RNA Viral genotype	> 100				
Viral markers										
Adinolfi, 1998	O: HCV+ Pts undergoing liver bx and HCV-RNA levels	36			HCV RNA					
Iijima, 2000	O: CHC Pts not receiving antiviral therapy	135			HCV core protein					
Kao, 1996	A: Pts w/ chronic persistent hepatitis B: Pts w/ CAH and/or liver cirrhosis C: Pts w/ HCC	34 30 30			HCV titer					
Papatheodoridis, 1997	O:Pts w/ chronic HCV	112			IgM anti HCV core					
Puoti, 1999	O: Anti-HCV+ Pts w/ persistently nl ALT	59	HAI: 0.8	HAI: 4	HCV RNA		Sp: 0.43*			
Miscellaneous										
Bayati, 1998	A: Pts w/ a nl AFP level of < 10. B: Pts w/ a high AFP level of >= 10.	125 75			AFP	17.8				98.6

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Chu, 2001	A: Chronic HCV Pts w/ elevated AFP	33			AFP					
	B: Chronic HCV Pts w/ nl AFP	82								

[a] Correlation coefficient: Pr = Pearson's r, Sp = Spearman's ρ, M = Multivariate, n/s = not specified
[b] p-value not reported for correlation coefficient
ns = no correlation coefficient given, but it was mentioned that the value was nonsignificant ($p>0.05$)
* Correlation coefficient is statistically significant ($p<0.05$)

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Extracellular matrix										
Casaril, 2000	A: CHC Pts	102			laminin		Sp: 0.44*			
	B: Healthy subjects w/ nl liver function tests and negative viral studies	81			P-III-P		Sp: 0.30*			
Di Costanzo, 1996	A: Responders to IFN alpha	22	HAI: 2.24		Laminin					
	B: Non-responders to IFN alpha	46	HAI: 2.75		P-III-P					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Fortunato, 2001	A: Pts w/ chronic HCV infection	54			Albumin ALP					
	B: Pts w/ cirrhosis from HCV infection	49			ALT Apo A1 Apo B AST AST/ALT ratio Cholesterol Direct Bili Fibronectin GPX LDII LDL MnSOD PCHE P-III-P Plts PT Total Bili					
Fukuda, 1998	O: Hemophilia Pts who had liver bx before IFN tx	36			HA type IV collagen		n/s: 0.78* n/s: 0.38*			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Fukuzaki, 2000	A: Complete response: ALT twice normal range (<40 IU/l) durring tx and maintained for 24 wks and HCV RNA- at 42 wks post tx	23			HA IV 7s PIIIP					
	B: Biochemical response: ALT twice normal range (<40 IU/l) durring tx and maintained for 24 wks and HCV RNA+ at 42 wks post tx	9								
	C: No response	46								
Gabrielli, 1997	A: Pts w/ chronic HCV infection	99			Laminin P-III-P	1.8 1.0			51.7 34.4	80 20.6
	B: Healthy controls	40								
Giannini, 2001	O: Pts w/ chronic HCV infection	109	Oth: 0.9	Oth: 6.5	P-III-P		Sp: 0.03*			
Guechot, 1994	A: Pts in cohort of ursodiol for PBC trial	78			HA GroupA HA GroupB				0.51 0.55	0.74 0.92
	B: Pts in trial of alpha-interferon for viral hepatitis C treatment	58			PIII NP GroupA PIII NP GroupB				0.62 0.4	0.77 0.66
	C: healthy controls	40								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Guechot, 1996	O: HCV+ pts	326			HA		Pr: 0.58*			
					HA	110		0.92	79.2	89.4
					HA	85		0.86	64.5	91.2
					P-III-P		Pr: 0.34*			
					P-III-P	0.8		0.69	70	63.4
					P-III-P	1.0		0.73	60	74
Ikeda, 2000	O: 205 consecutive Pts w/ CHC	205			gamma globulin	10 x 10^4 / mm^3	n/s: 0.57 [b]			
					gender	10 x 10^4 / mm^3	n/s: -0.21 [b]			
					HA	10 x 10^4 / mm^3	n/s: 0.42 [b]			
					Plts	10 x 10^4 / mm^3	n/s: -0.43 [b]		81.1	89.8
Ishibashi, 1996	A: Complete responders to IFN tx	49	HAI: 1.4	HAI: 6.3	HA		Sp: 0.51*			
					IV-75		Sp: 0.42*			
	B: Relapsers after IFN tx	36	HAI: 1.3	HAI: 6.4	P-III-P		Sp: 0.33*			
	C: Non-responders to IFN tx	36	HAI: 2.1	HAI: 7.7						
Jeffers, 1995	A: Pts w/ mild CAH	34			P-III-P	Abnormal			70	
	B: Pts w/ moderate-severe CAH	25			P-III-P	Abnormal			58	82
	C: Pts w/ cirrhosis	27								
Kasahara, 1997	A: IFN tx, sustained response	26	HAI: 2	HAI: 6.8	MMP-2		Sp: 0.26*			
	B: IFN tx, transient response	21	HAI: 1.7	HAI: 6.5	TIMP-1		Sp: 0.30*			
	C: IFN tx, no response	51	HAI: 2.3	HAI: 7.4						

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Lichtinghagen, 1999	A: Pts w/ CHC presenting to OP clinic B: Nl serum and plasma from healthy blood donors C: Livers explanted, but unable to transplant D: Cirrhotic liver from transplant pts				MMP-1 MMP-2 MMP-7					
Lichtinghagen, 2000	A: Healthy controls B: HCV+ Pts w/ chronic hepatitis C: HCV+ Pts w/ cirrhosis	20 40 20			MMP-2 MMP-9 Ratio of MMP-2:TIMP-1 TIMP-1 TIMP-2		Sp: ns Sp: ns Sp: -0.38 Sp: ns Sp: ns			
Lichtinghagen, 2001	A: Pts w/ CHC B: Pts w/ CHC and cirrhosis C: nl controls	29 7 10			MMP-7 MMP-9 TIMP-1 TIMP-2 TIMP-3 TIMP-4		Sp: 0.53* Sp: 0.39* Sp: 0.46* Sp: 0.34 ns Sp: 0.52*	0.75 0.67 0.76 0.66 0.55 0.72		
Lo Iacono, 1998	O: CHC virus Pts w/ recurring IFN tx	52	Sch: 1.6	HAI: 4.4	P-III-P sICAM-1 sVCAM-1	>10.57 >520 >1280		0.73 0.75 0.96	88.9 63.6 100	51.7 55.9 85.3

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
McHutchison, 2000a	O: Pts w/ CHC enrolled in a tx study for CHC	486	HAI: 1.5	HAI: 2.4	HA		n/s: 0.54*			
					HA	100			76	82
					HA	110			73	83
					HA	60			88	59
					HA	80			83	72
Murawaki, 1999	A: Pts w/ minimal chronic hepatitis.	24			7S collagen	8.5				85
					HA	100				93
	B: Pts w/ mild chronic hepatitis.	21			IV collagen	150				81
	C: Pts w/ moderate chronic hepatitis.	17			MMP-2	700 ng/mL				89
	D: Pts w/ liver cirrhosis	35								
	E: Pts w/ hepatocellular carinoma.	55								
	F: control Pts w/ no liver disease.	24								
Murawaki, 2001	O: Pts HCV + w/liver bx (fibrosis < F4)	165			Plts	14x10^4/mm^3			68	73
					Plts	16x10^4/mm^3			68	71
					Type IV Collagen	110 ng/ml			71	73
					Type IV Collagen	130 ng/ml			66	75

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Murawaki, 2001a	O: Pts w/ chroinc HCV w/o cirrhosis.	169			ALT	80			61	66
					HA	50			75	80
					HA	70			50	79
					IV-C7S	6			70	73
					IV-C7S	6.5			63	73
					MMP-2	550			75	70
					MMP-2	575			68	69
					P-III-NP	0.8			74	52
					P-III-NP	0.9			64	59
					TIMP-1	160			79	56
					TIMP-1	170			82	34
Ninomiya, 1998	A: IFN tx, complete response	16	MHAI: 3	MHAI:	HA after treatment		Sp: 0.56*			
	B: IFN tx, partial response	25	MHAI: 3.2	MHAI: 9.5						
	C: IFN tx, no response	8	MHAI: 3.5	MHAI:	HA before treatment		Sp: 0.61*			
					P-III-P after treatment		Sp: 0.51*			
					P-III-P before treatment		Sp: 0.53*			
					Type IV collagen after treatment		Sp: 0.32*			
					Type IV collagen before treatment		Sp: 0.24			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Ohashi, 1998	A: Pts who completely responded to IFN.	27			HA IV-C		0.49			
	B: Pts who did not respond to IFN.	35			P-III-P		0.53			
Plevris, 2000	A: Pts w/ liver disease caused by HCV infection	69			HA HA	100 200			72 67	95 98
	B: Pts w/ liver disease caused by alcohol				HA	300			47	100
	C: Pts w/ autoimmune liver disease									
	D: Pts w/ primary bilary cirrhosis									
	E: Pts w/ cryptogenic liver disease									
Serejo, 2001	A: Pts who were sustained responders.	44			P-III-P					
	B: Pts who were relapsers.	35								
	C: Pts who were non-responders.	38								
Ueno, 2001	A: Complete responders w/ bx done < 2 years after tx.	12			HA		Sp: 0.29*			
	B: Non-responders w/ bx done < 2 years after tx	24			P-III-P		Sp: 0.33*			
	C: Complete responders w/ bx done more than 2 years after tx	10			type IV collagen		Sp: 0.35*			
	D: Non-responders w/ bx done more than 2 years after tx	6								

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Verbaan, 1997	O: Pts w/ CHC infection	109			IgG		Sp: 0.43*			
					P-III-P	1.11	Sp: 0.32*		78	56
					type-IV collagen	250	Sp: 0.43*		87	75
Walsh, 1999	A: Pts w/ CHC infection	33			ALT	155		0.51	71	44
	B: Healthy controls	5			CIS P-III-P	0.8 U/mL		0.76*	50	85.7
					Orion P-III-P	4.2 ng/L		0.67	85	37.5
Walsh, 1999a	A: CHC w/ liver bx	43			ALT			0.59	67	52
	B: Healthy controls	19			MMP-2	860		0.67	69	59
					TIMP-1	500		0.73*	94	57
					TIMP-2	102		0.73*	85	47
Walsh, 2000	A: Pts w/ chronic HCV infection	37			ALT			0.54*		
					Laminin	1.26		0.82*	80	85.3
	B: Healthy controls	5			type IV collagen	148		0.85*	80	73.3
Wong, 1998	O: CHC virus Pts	130			ALT				76	48
					AST				48	39
					HA				86	88
Yamada, 1996	A: Pts who were complete responders to IFN tx.	9	Oth: 2.11		HA		Sp: 0.79*			
					P-III-P		Sp: 0.45*			
	B: Pts who were partial responders to IFN tx.	14	Oth: 1.78		type-IV collagen		Sp: 0.42*			
	C: Pts who were non-responders to IFN tx.	12	Oth: 7.08							

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Yamada, 1998	O: Japanese Pts w/ CHC and hemophilia	36	Desm: 1.9		HA type IV collagen		Sp: 0.78* Sp: 0.38*			
Cytokines/cytokine receptors										
Izzo, 1996	A: Pts w/ chronic HCV infection	123			IL-2R					
	B: Healthy HBV and HCV-controls	174								
Nutt, 2000	A: HCV + consecutive Pts w/ liver bx and nl ALT on >= 2 occasions	35	HAI: 4		ALT					
	B: HCV + consecutive Pts w/ liver bx and elevated ALT	35	HAI: 7							
Zylberberg, 1999	A: Pts w/ CHC B: Pts w/ chronic HBV C: Healthy control Pts	60 34			sTNF-R55 sTNF-R75 TNF-alpha					
Enzymes										
Anderson, 2000	O	133			AST/ALT ratio > 1				31	95
Assy, 2000	O: Pts w/ chronic HCV infection	79	Desm: 1.5	HAI: 3.5	ALT AST		M: 0.51* M: 0.64*			
Barbaro, 1996	A: Pts+ for HIV and HCV infection	55			CD4 plus T-cell count		Pr: 0.02			

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
	B: HCV+ pts C: Healthy controls	50 51			Plasma glutathione		Pr: 0.74*			
Choi, 1999	O: Pts w/ CHC infection	38			ALT HCV RNA					
Goldstein, 1999	O: CHC Pts given AFP, ALT testing, and liver bx	81			AFP ALT					
Gordon, 2000	A: ALT < 1.3 x nl in pts w/ HCV B: ALT > 1.3 x nl in pts w/ HCV	105 1639	MHAI: MHAI:	MHAI: MHAI:						
Haber, 1995	O: Pts w/ serologically confirmed HCV	90	HAI: 3.4		ALT/AST					
Healey, 1995	A: HCV+ normal AST B: HCV+ abnormal AST	19 23			AST					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Imbert-Bismut, 2001	A: CHC Pts tested in first year period	205			10 markers in logistic regression, group A			0.86		
	B: CHC Pts tested in second year, as confirmatory group	134			10 markers in logistic regression, group B			0.89		
					6 markers in logistic regression, group A			0.82		
					6 markers in logistic regression, group B			0.85		
Imperiale, 2000	O: A cohort of Pts w/ HCV.	177			AST/ALT	>1			56	90
Jamal, 1999	A: HCV Pts w/ nl ALT levels.	75	MHA I: 1.4		ALT					
	B: HCV Pts w/ abnl ALT levels.	200	MHA I:							
Kobayashi, 2000	O: consecutive Pts treated w/ alpha-IFN for 6 mos w/ f/u of 5 years	61			ALT					
Luo, 1998	O: 93 Pts w/ CHC.	93	Oth: 0.5	Oth: 7.7	ALT					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
					HCV RNA					
McCormick, 1996	O: Pts w/ CHC who were either treated or untreated and were biopsied.	44			ALT HCV titer		Sp: 0.49* Sp: 0.35			
Michielsen, 1997	O: CHC Pts	51			ALT AST		Sp: 0.08 Sp: 0.29*			
Ono, 1999	O: Pts w/ chronic HCV infection	435			ALB Alkaline phosphatase ALT AST GTP LDH Plts PT total Bili WBC	> 4 vs. < 4 1IV 1IV 104 1%				
Park, 2000	O: Pts w/ CHC	153			AST/ALT	1			46.7	95.9

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Poynard, 1997	O: Pts w/ chronic HCV infection	500			Age AST Bili Body weight Creatinine GGT IDU Index: age, Plts Plts PT			0.79		
Sheth, 1998	A: Ratio of AST to ALT >= 1 in Pts w/ CHC B: Ratio of AST to ALT <= 1 in Pts w/ CHC				AST/ALT	> 1				100
Shima, 2000	O: Pts w/ chronic HCV infections w/ sustained response to IFN tx	36	HAI: 2	HAI: 8	Cholinesterase Plts Total bile acid Zinc sulphate turbidity test					
Stanley, 1996	A: Pts w/ chronic HCV infection and nl ALT B: Pts w/ chronic HCV infection and elevated ALT	15 85			ALT	> normal	Sp: ns			
Tsushima, 1999	A: Pts receiving IFN tx. B: Pts not receiving IFN tx.	43 10	Oth: 1 Oth: 2		ALT/AST					

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Yeo, 2001	O: Pts w/ chronic HCV infection	60			ALT HCV-RNA Viral genotype	> 100				
Viral markers										
Adinolfi, 1998	O: HCV+ Pts undergoing liver bx and HCV-RNA levels	36			HCV RNA					
Iijima, 2000	O: CHC Pts not receiving antiviral therapy	135			HCV core protein					
Kao, 1996	A: Pts w/ chronic persistent hepatitis B: Pts w/ CAH and/or liver cirrhosis C: Pts w/ HCC	34 30 30			HCV titer					
Papatheodoridis, 1997	O:Pts w/ chronic HCV	112			IgM anti HCV core					
Puoti, 1999	O: Anti-HCV+ Pts w/ persistently nl ALT	59	HAI: 0.8	HAI: 4	HCV RNA		Sp: 0.43*			
Miscellaneous										
Bayati, 1998	A: Pts w/ a nl AFP level of < 10. B: Pts w/ a high AFP level of >= 10.	125 75			AFP	17.8				98.6

Evidence Table 8: Results of studies evaluating biochemical tests and serologic measures of fibrosis that may predict findings of liver biopsy (continued)

Author, Year	Study Groups	N	Staging System: mean	Grading System: mean	Serologic Measure	Threshold Value	Statistical Tests of Relation to Biopsy Findings: Correlation Coefficient [a]	ROC	Sensitivity	Specificity
Chu, 2001	A: Chronic HCV Pts w/ elevated AFP	33			AFP					
	B: Chronic HCV Pts w/ nl AFP	82								

[a] Correlation coefficient: Pr = Pearson's r, Sp = Spearman's ρ, M = Multivariate, n/s = not specified
[b] p-value not reported for correlation coefficient
ns = no correlation coefficient given, but it was mentioned that the value was nonsignificant ($p>0.05$)
* Correlation coefficient is statistically significant ($p<0.05$)

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of current treatment options in naïve patients					
Pegylated interferon/ribavirin combination therapy					
Glue, 2000	France	72	ALT: 1 abnl result w/i past 6 mos, detectable HCV in serum, "adult" age, initial liver bx, nl Bili, nl Alb, nl Cr, nl fasting blood sugar, nl TSH, nl AFP, nl hematologic parameters, nl PT, antibody titers <1:160	IFN + RBV, HBV+, decompensated liver disease, depression, other psychiatric illness, RBV monotherapy, liver disease of other etiology, IFN monotherapy, any clinical trial or investigational drug w/i 30 ds prior, HIV+	To assess the safety, pharmacokinetics, and efficacy of peg-IFN alpha-2b plus RBV in pts w/ CHC
Manns, 2001	United States Canada Europe Argentina	1530	ALT >34 for women and >43 for men, detectable HCV in serum, nl Cr, initial liver bx w/CHC in past year, tx naïve, WBC >13, neutrophil >1.5, Hgb 12 for women and 13 for men, plts >100,000, nl Bili, nl Alb	HIV+, immune suppression, depression, other psychiatric illness, decompensated liver disease, comorbidities: cardiovascular, neurologic or hematologic, no contraception, AFP >50 mg/L, DM	To assess the safety and efficacy of two different regimens of Peg IFN and RBV compared w/ IFN alpha 2b and RBV and identify predictors and response for peg IFN alpha 2b.

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Pegylated interferon monotherapy					
Heathcote, 2000	United States Canada	271	ALT, initial liver bx	AFP >100 ng/y, plts <75,000, WBC <500, IFN monotherapy, presence of any other liver disease, comorbidities: malignancy, GI, neurologic, or cardiovascular, HIV+, depression, psychiatric illness, decompensated liver disease	To compare the efficacy and safety of two doses of peg-IFN alpha-2a, given once wkly, w/ the safety and efficacy of a standard regimen of unmodified IFN alpha-2a in pts w/ HCV and cirrhosis or fibrosis.
Lindsay, 2001	United States Europe Australia	1299	U/S: no mass lesion, detectable HCV in serum, initial liver bx w/i 1 y of enrollment, AFP w/i nl limits, ALT el >= 1 time w/i 6 mo of enrollment, WBC >4, neutrophil >1.8, Hgb >12 in females and >13 in males, plts > 130,000/mm^3	Hemophilia, breast feeding, illicit drug use, HBV+, HCC, pregnancy, HIV+, active IDU, hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, EtOH, NASH, any antiviral therapy, hemoglobinopathy, other medical conditions that could interfere with participation, any prior tx, autoimmune hepatitis	To evaluate the efficacy of pegIFN alpha 2b compared w/ IFN alpha 2b in tx-naïve pts w/ CHC

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Reddy, 2001	United States	158	HCV+, detectable HCV in serum, initial liver bx w/i prior 12 mo	Neurologic comorbidity: seizure disorder, IDU, other illicit drug use, presence of bridging fibrosis, presence of cirrhosis, non-response to previous therapy, pregnancy, depression, other psychiatric illness, EtOH in the past 12 mo, any antiviral therapy, cardiovascular comorbidity, other comorbidities: retinopathy, unstable thyroid dysfunction, renal or liver disease from any other cause, WBC <1500, plts 70,000, Cr 1.5x U/L of nl range, any treatment for HCV	To evaluate safety and efficacy of four doses of once-wkly peg-(40 kD) IFN alpha-2a administered for 48 wks, compared w/ 3 mu of IFN alpha-2a tiw. The study intends to establish the most appropriate dose of Peg (40 kD) IFN alpha-2a for larger trials.
Zeuzem, 2000a	Canada Europe Australia	531	HCV+, detectable HCV in serum: RNA >2000 copies per mL, el ALT on >=2 occasions in previous 6 mo, initial liver bx w/ hepatitis, liver bx findings consistent with CHC, adults	Malignancy, decompensated liver disease, HBV+, immune suppression, depression, other psychiatric illness, HIV+, hepatitis A infection, other comorbidities: seizure, neurologic OR cardiovascular, AFP >25 ng/mL, chronic pulmonary disease, autoimmune disorder, unwillingness to practice contraception, severe retinopathy, IFN monotherapy, neutrophil <1500, plts <90,000, Cr 1.5x UL of nl	To compare the efficacy and safety of peg-IFN alpha-2a administered once per wk w/ the efficacy and safety of IFN alpha-2a tiw for 48 wks.

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Interferon/ribavirin combination therapy					
Berg, 2000	Germany	185	El ALT, any previous treatment, HCV+, detectable HCV in serum	Psychiatric illness, acute or chronic IDU, HBV+, decompensated liver disease, acute or chronic EtOH, immune suppression, plts <100 nl, depression, HIV+, severe concurrent diseases, Hgb <11 g/dL, pregnancy	To examine if 12 wk combination therapy is more effective in improving initial and SVR compared w/ IFN monotherapy in untreated pts. pts who achieved a virologic response were treated w/ IFN alpha monotherapy for an additional 40 wks and then SVR was evaluated 24 wks after end of tx
el-Zayadi, 1999	Egypt	52	Hgb >12, ALT el for 6 mo, U/S w/absence of focal hepatic lesion, initial liver bx, HCV+, HCV genotype 4	Contraindication to IFN, decompensated liver disease, HCV genotype 1, 2, or 3	To asses the efficacy of IFN alpha 2b alone and w/ RBV as initial therapy in male Egyptian pts w/ CHC, genotype 4.
Ferenci, 2001	Austria		Hgb >12 for males and >13 for females, WBC >3000, ALT 1.5x nl for >=6 mos, initial liver bx w/i 1 yr prior, detectable HCV in serum, plts >100,000, age 19-65 yrs	HIV+, EtOH, IDU, sexually active women refusing contraception, HBV+, decompensated liver disease, pregnancy or breast feeding, depression, other psychiatric illness, cardiovascular comorbidity: CHD, DM, autoimmune disorders, any unstable medical condition	To test two different schedules of high-dose induction therapy w/ IFN in combination w/ RBV, compared w/ a standard IFN/RBV combination therapy

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Mangia, 2001	Italy	192	Detectable HCV in serum, ALT available for 6 mo, initial liver bx	DM, HBV+, decompensated liver disease: ascites, bleeding varices, and encephalopathy, pregnancy, depression, EtOH, HIV+, plts <100,000, autoimmune disorder, significant medical illness, IFN monotherapy, WBC <3500, Hgb <12 for females and <13 for males, other psychiatric illness	To compare the efficacy of a high dose regimen of IFN alpha2B (5 mu tiw) for 12 mos alone or in combination w/ RBV for the tx of naïve pts w/ CHC. Secondary aims were to evaluate the effects of baseline features on the response to therapy and to determine a reliable point in time during tx to predict non response.
Studies of interferon/amantadine combination therapy, with or without ribavirin					
Caronia, 2001	United Kingdom	179	Age: 18-70, HCV+, detectable HCV in serum, no previous tx, CHC on initial liver bx, ALT 1.3x UL of nl w/i last 6 mos	EtOH >28 units/wk, active IDU, HBV+, liver disease of any other etiology, High ceruplasmin, serum autoantibody titer >1:40	To assess the efficacy of combination therapy w/ IFN alpha and amantadine compared to IFN monotherapy in previously untreated pts w/ CHC

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Helbling, 2002	Switzerland	246	Tx naïve, HCV proven by bx w/i prior 2 yrs, detectable HCV in serum, Cr <1.5x UL of nl, age 18-65 yrs	Decompensated liver disease, HIV+, depression, other psychiatric illness, pregnancy, refusal to use contraception, presence of fibrosis: 28 Child-Pugh points, HBV+, illicit drug use w/i 1 yr of study, EtOH >20 g/d for females and >40 g/d for males, immune suppression, psychosocial instability, lactation, comorbidity: cardiovascular, neurologic, hematologic, pulmonary, renal, metabolic, rheumatologic, or malignancy, U/S: focal lesion w/i 1 mo of tx, WBC <2000, plts >50,000, TSH el, AFP above nl, IFN	To clarify in a large, double-blind randomized placebo-controlled trial the efficacy, safety and cost-effectiveness of amantadine and IFN alpha for tx of naïve pts w/ CHC
Mangia, 2001a	Italy	200	Detectable HCV in serum, initial liver bx, el ALT for 6 mos	EtOH, current IDU, depresson, other psychiatric illness, HBV+, decompensated liver disease, plts <100,000, HIV+, DM, significant medical illness, WBC <3,500, immune suppression	To assess the efficacy and safety of IFN+amantadine compared to IFN monotherapy in naïve pts w/ CHC

Evidence Table 9: Overall summary of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Tabone, 2001	Italy	180	Detectable HCV in serum, HCV+, CHC w/o cirrhosis on initial liver bx, ALT 1.5x UL of nl in 3 lab draws	Chronic EtOH, active IDU, other illicit drug use, depression, other psyciatric illness, HBV+, HIV+, pregnancy, neurologic comorbidity, hematologic comorbidity, cardiovascular comorbidity, autoimmune disease, metabolic disease, renal disase, WBC <2,500, plts <100,00	To assess the efficacy and tolerability of IFN + amantadine in the tx of CHC
Zeuzem, 2000	Germany	120	HCV+, age >18 and <70 y, presence of fibrosis: CHC on liver bx, initial liver bx w/i 1 y, el ALT for >=6 mo before tx, WBC >2500, plts >70,000	EtOH >50 g/d of ethanol, IDU w/i previous year, GI comorbidity, immune suppression: organ transplant or autoimmune disorder, psychiatric illness, HIV+, HBV+, cardiovascular comorbidity, pregnancy, neurologic comorbidity, malignancy comorbidity, anaphylactic allergy to IFN, other comorbidities: liver disease from another cause OR renal disease OR rheumatologic disease, other viral infections: systemic bacterial or fungal infection, lactation, IFN + RBV, IFN monotherapy, amantadine, hematologic comorbidity	To compare the efficacy, safety, and health related quality of life of IFN alpha alone or in combination w/ amantadine for tx of CHC.

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of current treatment options in naive patients									
Pegylated interferon/ribavirin combination therapy									
Glue, 2000	RCT	IFN: peg-IFN2b, .35 ug/kg, qw, 24 wks RBV: 600-800 mg qd, 24 wks	12						
		IFN: peg-IFN2b, .7 ug/kg, qw, 24 wks RBV: 600-1200 mg qd, 24 wks	18						
		IFN: peg-IFN2b, 1.4 ug/kg, qw, 24 wks RBV: 600-1200 mg qd, 24 wks	18						
		IFN: peg-IFN2b, .35 ug/kg, qw, 24 wks	6						
		IFN: peg-IFN2b, .7 ug/kg, qw, 24 wks	9						
		IFN: peg-IFN2b, 1.4 ug/kg, qw, 24 wks	9						

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Manns, 2001	RCT									
		IFN: peg-IFN2b, 1.5 mg/kg, qw, 48 wks	511	43				S3 29		
				62.8		Kno	7.9			
		RBV: 800 mg qd, 48 wks							1	68.10
									2, 3	28.96
									4,5,6	3.13
		IFN (initial): peg-IFN2b, 1.5 mg/kg, qw, 4 wks	514	44				S3 30		
				66.1		Kno	7.9			
		IFN (maintenance): peg-IFN2b, 0.5 mg/kg, qw, 44 wks							1	67.90
									2, 3	29.96
		RBV: 1000-1200 mg qd, 48 wks							4,5,6	2.33
		IFN: alpha-2b, 3 mu tiw, 48 wks	505	43				S3 28		
		RBV: 1000-1200 mg qd, 48 wks		66.5		Kno	7.8			
									1	67.92
									2, 3	28.91
									4,5,6	3.17

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Pegylated interferon monotherapy										
Heathcote, 2000	RCT									
		IFN: alpha-2a, 3 mu tiw, 48 wks	88	46.9 70.5 C: 87.5, B: 5.68, A: 3.40, O: 3.40	76	HAI	12.8		104.1 1a 1b 2 3 4 not specified	 31.82 21.59 13.64 30.68 0.00 2.27
		IFN: peg-IFN2a, 90 mg, qw, 48 wks	96	47.2 74.0 C: 90.6, B: 1.04, A: 2.08, O: 6.25	79	HAI	12.7		104.1 1a 1b 2 3 4 not specified	 28.13 32.29 7.29 27.08 2.08 3.13
		IFN: peg-IFN2a, 180 mg, qw, 48 wks	87	47.1 72.4 C: 86.2, B: 5.74, A: 2.29, O: 5.74	79	HAI	13.4		123.3 1a 1b 2 3 4 not specified	 37.93 17.24 16.09 22.99 1.15 4.60

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Lindsay, 2001	RCT								
		IFN: peg-IFN2b, 0.5 ng/kg, qw, 48	315	43.1	3	HAI	A 6.8		
		wks		58.7		HAI	S 1.4		18.5
				C: 90.1					1 67.30
									2 11.11
									3 16.83
									other 4.76
		IFN: peg-IFN2b, 1.0 ng/kg, qw, 48	297	43.7	3	HAI	A 6.9		
		wks		63.3		HAI	S 1.4		20.4
				C: 90.9					1 67.00
									2 10.10
									3 17.85
									other 5.05
		IFN: peg-IFN2b, 1.5 ng/kg, qw, 48	304	42.9	4	HAI	A 6.7		
		wks		62.5		HAI	S 1.3		19.2
				C: 94.0					1 73.36
									2 10.53
									3 13.49
									other 2.63
		IFN: alpha-2b, 3 mu tiw, 48 wks	303	42.6	4	HAI	A 7.1		
				68.3		HAI	S 1.4		18.6
				C: 89.1					1 71.62
									2 9.24
									3 17.49
									other 1.65

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Reddy, 2001	RCT									
		IFN: alpha-2a, 3 mu tiw, 48 wks	33	41.8 78.8 C: 78.7, B; 12.1, A: 3.03, O: 6.06		HAI	10.8		1 non-1 unknown	81.82 15.15 3.03
		IFN: peg-IFN2a, 45 µg, qw, 48 wks	20	41.9 65.0 C: 90, B: 10, A: 0, O: 0		HAI	11.7		1 non-1 unknown	75.00 25.00 0.00
		IFN: peg-IFN2a, 90 µg, qw, 48 wks	20	43.1 70.0 C: 95, B: 0, A: 5, O: 0		HAI	10.6		1 non-1 unknown	70.00 30.00 0.00
		IFN: peg-IFN2a, 180 µg, qw, 48 wks	45	42 82.2 C: 88.8, B: 8.88, A: 0, O: 2.22		HAI	10.7		1 non-1 unknown	77.78 22.22 0.00
		IFN: peg-IFN2a, 270 µg, qw, 48 wks	41	41.6 85.4 C: 87.8, B: 9.75, A: 0, O: 2.43		HAI	10		1 non-1 unknown	63.41 29.27 7.32

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Zeuzem, 2000a	RCT									
		IFN (initial): peg-IFN2a, 180 µg, qw, 48 wks	267	40.5 66.7 C: 86.1, B: 2.24, A: 8.98, O: 2.62		HAI	8.6	A1 65.0 A2 30.0 A3 3.3 S1 88.4 S3 7.1	1a 1b 1b 2 3 4 not specified	29.96 32.96 32.96 9.36 25.47 1.87 0.37
		IFN (initial): alpha-2a, 6 mu tiw, 12 wks IFN (maintenance): alpha-2a, 3 mu, tiw, 36 wks	264	41 66.7 C: 84.8, B; 1.89, A: 9.84, O: 3.40		HAI	3.4	A1 60.0 A2 40.0 A3 0.0 S1 84.8 S1 84.8 S3 4.9	1a 1b 1b 2 3 4 not specified	31.44 29.55 29.55 12.88 23.86 1.14 1.14

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Interferon/ribavirin combination therapy									
Berg, 2000	RCT								
		IFN: alpha-2a, 6 mu tiw, 12 wks	93	42		HAI	S 1.5		70
		RBV: 7 mg/kg, bid, 12 wks		57.0					15.2
									1a 24.73
									1a/b 1.08
									1b 47.31
									2a 2.15
									2a/c 1.08
									2b 3.23
									3a 18.28
									4 2.15
		IFN: alpha-2a, 6 mu tiw, 12 wks	92	42		HAI	S 1.5		82
				55.4					14.7
									1a 20.65
									1a/b 1.09
									1b 54.35
									2a 2.17
									2a/c 1.09
									2b 1.09
									3a 17.39
									4 2.17
el-Zayadi, 1999									
		IFN: alpha-2b, 3 mu tiw, 24 wks	26	42		HAI	S 5.0		116
		RBV: 1000 mg qd, 24 wks		100.0		HAI	T 9.4		
		IFN: alpha-2b, 3 mu tiw, 24 wks	26	39		HAI	S 5.0		123

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
				100.0		HAI	T 9.7			
Ferenci, 2001	RCT									
		IFN (initial 1): alpha-2b, 10 mu, qd, 2 wks IFN (initial 2): alpha-2b, 10 mu, qed, 12 wks IFN (maintenance): alpha-2b, 5 mu, qed, 24 wks RBV: 1000-1200 mg qd, 38 wks	130	39.4 73.8					68 1a 1b 2 3a 4	22.31 50.77 1.54 23.85 1.54
		IFN (initial): alpha-2b, 5 mu, qd, 14 wks IFN (maintenance): alpha-2b, 5 mu, qed, 24 wks RBV: 1000-1200 mg qd, 38 wks	124	42.8 70.2					66 1a 1b 2 3a 4	14.52 53.23 3.23 23.39 5.65
		IFN: alpha-2b, 5 mu, qed, 38 wks RBV: 1000-1200 mg qd, 38 wks	119	39.9 66.4					79 1a 1b 2 3a 4	18.49 43.70 4.20 26.89 6.72

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Mangia, 2001	RCT									
		IFN: alpha-2b, 5 mu tiw, 12 mos	96	49		Sch		A>1 19.8		
				71.9		Sch		A0,1 80.2	8	
						Sch		S1,2 93.8	1b	53.13
						Sch		S3 6.2	2a	33.33
									3	9.38
									other	4.17
		IFN: alpha-2b, 5 mu tiw, 12 mos	96	46		Sch		A>1 26.0		
		RBV: 1000-1200 mg qd, 12 mos		61.5		Sch		A0,1 74.0	7	
						Sch		S1,2 89.6	1b	41.67
						Sch		S3 10.4	2a	35.42
									3	17.71
									other	5.21

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of interferon/amantadine combination therapy, with or without ribavirin										
Caronia, 2001	RCT									
		IFN (Pilot study): alpha-2a, 4.5 mu, tiw, 48 wks	18	42	0				1	55.56
		Amantadine (Pilot study): 200 mg, qd, 48 wks IFN (Pilot study): alpha-2a, 4.5 mu, tiw, 48 wks	18	40	0				1	50.00
		IFN (Multicenter): alpha-2a, 4.5 mu, tiw, 48 wks	71	42	10				1	28.17
		Amantadine (Multicenter): 200 mg, qd, 48 wks IFN (Multicenter): alpha-2a, 4.5 mu, tiw, 48 wks	72	43	8				1	26.39
		IFN (Combined): alpha-2a, 4.5 mu tiw, 48 wks	89	42					1	33.71
		Amantadine (Combined): 200 mg, qd, 48 wks IFN (Combined): alpha-2a, 4.5 mu tiw,	90	41	7				1	31.11

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		48 wks								
Helbling, 2002	RCT									
		Amantadine: 100 mg, bid, 52 wks	125	39				A1 47.2	101	
		IFN (initial): alpha-2a, 6 mu tiw, 20 wks		65.6				A2 34.4 A3 14.4	1	52.80
		IFN (maintenance): alpha-2a, 3 mu, tiw, 32 wks						S1-S2 26.4 S3 64.8 S4 4.8	2 3 4	9.60 27.20 4.00
									6	0.80
		Amantadine (initial): Placebo	121	38				A1 52.1	111	
		IFN (initial): alpha-2a, 6 mu tiw, 20 wks		72.7				A2 40.5 A3 9.9	1	42.98
		IFN (maintenance): alpha-2a, 3 mu, tiw, 32 wks						S1-S2 24.0 S3 75.2 S4 3.3	2 3 4	9.09 41.32 4.96
Mangia, 2001a	RCT									
		IFN (initial): alpha-2a, 6 mu tiw, 12 mos	101	48		HAI		S0-3 48.5		
				70.3		HAI		S1-3 51.5	7.1	
									1	59.41
									2a	25.74
									3	10.89
									4	3.96
		Amantadine (initial): 100 mg, bid, 12 mos	99	46		HAI		S0-3 36.4		
				61.6		HAI		S1-3 63.6	7.1	
		IFN (initial): alpha-2a, 6 mu tiw, 12 mos							1	52.53
									2a	34.34
									3	7.07

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									4	6.06
Tabone, 2001	RCT									
		IFN (initial): alpha-2a, 6 mu, qed, 6 mos	90	44 66.7					114	
		IFN (maintenance): alpha-2a, 3 mu, qed, 6 mos							1/4 2/3	58.89 41.11
		Amantadine: 100 mg, bid, 12 mos	90	42					103	
		IFN (initial): alpha-2a, 6 mu, qed, 6 mos		62.2					1/4	52.22
		IFN (maintenance): alpha-2a, 3 mu, qed, 6 mos							2/3	47.78
Zeuzem, 2000	RCT									
		Amantadine: 100 mg, Twice a day, 48 wks	60	42.1 61.7						
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks							1 2	70.00 5.00
		IFN (maintenance): alpha-2a, 3 mu, tiw, 24 wks							3 4	21.67 1.67
		IFN (initial): alpha-2a, 6 mu tiw, 24 wks	60	41.6 60.0						
		IFN (maintenance): alpha-2a, 3 mu, tiw, 24 wks							1 2 3	66.67 5.00 25.00

Evidence Table 10: Characteristics of patients in randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
									4 1.67

Evidence Table 11: Methodologic quality of randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Pegylated interferon/ribavirin combination therapy							
Glue, 2000	63	33	100	85	0	0	56
Manns, 2001	100	83	75	80	88	50	85
Pegylated interferon monotherapy							
Heathcote, 2000	100	67	50	70	83	50	74
Lindsay, 2001	88	83	100	85	100	50	91
Reddy, 2001	63	75	50	70	83	50	68
Zeuzem, 2000a	100	50	75	70	100	100	79
Interferon/ribavirin combination therapy							
Berg, 2000	88	67	75	85	83	0	80
el-Zayadi, 1999	38	50	50	85	33	0	51
Ferenci, 2001	88	33	50	70	75	0	63
Mangia, 2001	75	83	50	60	100	0	74

Evidence Table 11: Methodologic quality of randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of interferon/amantadine combination therapy, with or without ribavirin							
Caronia, 2001	88	67	50	85	17	50	61
Helbling, 2002	100	100	75	75	100	50	90
Mangia, 2001a	88	67	75	85	100	50	83
Tabone, 2001	88	67	75	85	83	100	80
Zeuzem, 2000	100	100	100	60	100	50	92

Evidence Table 11: Methodologic quality of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 6 points. This included whether assignment of patients to study groups was randomized (2 points); whether groups had any differences in key patient characteristics (2 points); and whether clinicians, patients, and outcome assessors were blinded (2 points).

[c] ***Description of Therapy/Management***: The total maximum score was 4 points. This included sufficiently detailed description of the treatment regimen (2 points); and description of other treatments or tests given to subjects (2 points).

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 8 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); whether adjustment of potential confounders were multi-variate or stratified analyses and coding of confounders (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of current treatment options in naïve patients								
	Pegylated interferon/ribavirin combination therapy							
Glue, 2000	A IFN: peg-IFN2b, 0.35 ug/kg, qiw, 24 wks			58[a]	17[a]			
6 mos.	RBV: 600-800 mg qd, 24 wks							
	B IFN: peg-IFN2b, 0.7 ug/kg, qiw, 24 wks			69[a]	53[a]			
	RBV: 600-1200 mg qd, 24 wks							
	C IFN: peg-IFN2b, 1.4 ug/kg, qiw, 24 wks			81[a]	60[a]			
	RBV: 600-1200 mg qd, 24 wks							
	D IFN: peg-IFN2b, 0.35 ug/kg, qiw, 24 wks			50[a]	0[a]			
	E IFN: peg-IFN2b, 0.7 ug/kg, qiw, 24 wks			63[a]	44[a]			
	F IFN: peg-IFN2b, 1.4 ug/kg, qiw, 24 wks			50[a]	42[a]			
Manns, 2001	A IFN: peg-IFN2b, 1.5 mg/kg, qiw, 48 wks	65	54	65*	54*	14	2.7	8.3
6 mos.	RBV: 800 mg qd, 48 wks							
	B IFN (initial): peg-IFN2b, 1.5 mg/kg, qiw, 4 wks	63	48	56	47	13	2.5	7.0
	IFN (maintenance): peg-IFN2b, 0.5 mg/kg, qiw, 44 wks							
	RBV: 1000-1200 mg qd, 48 wks							
	C IFN: alpha-2b, 3 mu tiw, 48 wks	69	47	54*	47*	13	2.6	6.7

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
	RBV: 1000-1200 mg qd, 48 wks							
	Pegylated interferon monotherapy							
Heathcote, 2000	A IFN: alpha-2a, 3 mu tiw, 48 wks	22*†	15*	14*†	8.0*	31*[a]	8	14
6 mos.	B IFN: peg-IFN2a, 90 µg, qiw, 48 wks	35*	20	42*	15	44[a]	7	9
	C IFN: peg-IFN2a, 180 µg, qiw, 48 wks	39†	34*	44*†	30*	54*[a]	13	10
Lindsay, 2001	A IFN: peg-IFN2b, 0.5 ng/kg, qiw, 48 wks	25 [c]	17 §[c]	33 §	18 §	20	2.9	2.9
6 mos.	B IFN: peg-IFN2b, 1.0 ng/kg, qiw, 48 wks	31 [c]	24 §[c]	41 §	25 §	19	3.7	4.7
	C IFN: peg-IFN2b, 1.5 ng/kg, qiw, 48 wks	26 [c]	18 §[c]	39 §	23 §	15	2.3	4.9
	D IFN: alpha-2b, 3 mu tiw, 48 wks	20[c]	12[R c]	24[R]	12[R]	13	2.0	2.0
Reddy, 2001	A IFN: alpha-2a, 3 mu tiw, 48 wks	15	9.0*†	12*†	3.0*†	57[a]	9	
6 mos.	B IFN: peg-IFN2a, 45 ug, qiw, 48 wks	20	10	30	10	47[a]	10	
	C IFN: peg-IFN2a, 90 ug, qiw, 48 wks	20	25	45	30	59[a]	0	
	D IFN: peg-IFN2a, 180 ug, qiw, 48 wks	38	38*	60	36*	63[a]	22	
	E IFN: peg-IFN2a, 270 ug, qiw, 48 wks	27	27†	56†	29†	66[a]	20	

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Zeuzem, 2000a	A IFN (initial): peg-IFN2a, 180 mcg, qiw, 48 wks	46	45*	69*	39*	63[a]	7	20
6 mos.	B IFN (initial): alpha-2a, 6 mu tiw, 12 wks IFN (maintenance): alpha-2a, 3 mu tiw, 36 wks	39	25	28*	19*	55[a]	10	18
	Interferon/ribavirin combination therapy							
Berg, 2000	A IFN: alpha-2a, 6 mu tiw, 12 wks			37*	26		2	24*
6 mos.	RBV: 7 mg/kg, bid, 12 wks							
	B IFN: alpha-2a, 6 mu tiw, 12 wks			29*	17		3	7*
el-Zayadi, 1999	A IFN: alpha-2b, 3 mu tiw, 24 wks	62*	38*	35*	19	56[a]	3.8	35
6 mos.	RBV: 1000 mg qd, 24 wks							
	B IFN: alpha-2b, 3 mu tiw, 24 wks	69*	15*	11*	8	46[a]	3.8	0

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Ferenci, 2001	A IFN (initial 1): alpha-2b, 10 mu, qd, 2 wks	54	50.8	55.3	48.5			7
6 mos.	IFN (initial 2): alpha-2b, 10 mu, every other day, 12 wks							
	IFN (maintenance): alpha-2b, 5 mu, every other day, 24 wks							
	RBV: 1000-1200 mg qd, 38 wks							
	B IFN (initial): alpha-2b, 5 mu, qd, 14 wks	54	41.1	48.4	40.3			10
	IFN (maintenance): alpha-2b, 5 mu, every other day, 24 wks							
	RBV: 1000-1200 mg qd, 38 wks							
	C IFN: alpha-2b, 5 mu, every other day, 38 wks	56	41.1	50.4	40.3			9
	RBV: 1000-1200 mg qd, 38 wks							
Mangia, 2001	A IFN: alpha-2b, 5 mu tiw, 12 mos	40*	23*	34*	21*		8.3	
6 mos.	B IFN: alpha-2b, 5 mu tiw, 12 mos	69*	57*	59*	54*		10.4	
	RBV: 1000-1200 mg qd, 12 mos							

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of interferon combination therapy with amantadine, with or without ribavirin								
	Studies of naïve patients							
Caronia, 2001	A IFN (Pilot study): alpha-2a, 4.5 mu tiw, 48 wks			33[c]	29[c]			
	B Amantadine (Pilot study): 200 mg qd, 48 wks IFN (Pilot study): alpha-2a, 4.5 mu tiw, 48 wks			54[c]	50[c]			
	C IFN (Multicenter): alpha-2a, 4.5 mu tiw, 48 wks			17[c]	15[c]			
	D Amantadine (Multicenter): 200 mg qd, 48 wks IFN (Multicenter): alpha-2a, 4.5 mu tiw, 48 wks			25[c]	18[c]			
	E IFN (Combined): alpha-2a, 4.5 mu tiw, 48 wks			19[c]	17[c]			
	F Amantadine (Combined): 200 mg qd, 48 wks IFN (Combined): alpha-2a, 4.5 mu tiw, 48 wks			31[c]	23[c]			
Helbling, 2002 6 mos.	A Amantadine: 100 mg, bid, 52 weeks IFN (initial): alpha-2a, 6 mu tiw, 20 weeks IFN (maintenance): alpha-2a, 3 mu tiw, 32 weeks	28.9	25.6	30.6	20.7		11.2	24
	B IFN (initial): alpha-2a, 6 mu tiw, 20 weeks IFN (maintenance): alpha-2a, 3 mu tiw, 32 weeks	29.6	20.8	28.8	13.6		8.8	18.4

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Mangia, 2001a	A IFN (initial): alpha-2a, 6 mu tiw, 12 mos	34.6	18.8*	28.7*	16.8*		8.0	
	B IFN (initial): alpha-2a, 6 mu tiw, 12 mos Amantadine (initial): 100 mg, bid, 12 mos	46.5	36.4*	45.5*	29.3*		7.1	
Tabone, 2001	A IFN (initial): alpha-2a, 6 mu, qed, 6 mos IFN (maintenance): alpha-2a, 3 mu, qed, 6 mos			37[c]	17[c]			
	B Amantadine: 100 mg, bid, 12 mos IFN (initial): alpha-2a, 6 mu, qed, 6 mos IFN (maintenance): alpha-2a, 3 mu, qed, 6 mos			47[c]	24[c]			
Zeuzem, 2000 6 mos.	A Amantadine: 100 mg, bid, 48 wks IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 3 mu tiw, 24 wks	37	20	33	17		7	2
	B IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 3 mu tiw, 24 wks	35	25	33	37		3	8

Evidence Table 12: Results of randomized controlled trials of current treatment options for chronic hepatitis C (continued)

[a] Percentage based on a denominator different from the group N
[c] Complete response, defined as combined virological and biochemical response
* $p < 0.05$ for the pairwise comparison between two groups marked with this symbol
† $p < 0.05$ for the pairwise comparison between two groups marked with this symbol

[§] $p < 0.05$ for the comparison groups marked with this symbol and the group marked [R]
[R] Reference group for comparison

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of current treatment options in nonresponders/relapsers to prior therapy					
Studies of nonresponders					
Barbaro, 1999	Italy	200	IFN monotherapy >3 and/or <6 mo, IFN alpha-2b prior to study (not <3 mo and not >6 mo) and were nonresponders (no biochemical and viral response at end of tx), age <18 y, nonresponse to previous therapy: defined as ALT/HCV response from previous tx, detectable HCV in serum, HCV+, EtOHism	Hepatitis delta infection, decompensated liver disease, HBV+, DM, immune suppression, HIV+, other viral infections: EBV, CMV, and mycobacterial, cardiomyopthies, neurologic comorbidity, malignancy comorbidity, pregnancy, Wilson's disease, PT >5 sec longer than nl, Cr 2x nl, Bili >3x nl, Hgb <10 g/dL, neutrophil <1000, hypertension, use of hepatotoxic drugs in past 6 mo, malnutrition, hemochromatosis, alpha-1-antitrypsin, autoimmune hepatitis, neoplastic disease, metabolic disorder, other comorbidity: malnutrition, WBC <2500	Randomized controlled trial assessing clinical efficacy of IV recombinant IFN-beta compared w/ IFN-alpha-2b + RBV in pts w/ CHC unresponsive to IFN-alpha-2b at standard doses.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Bresci, 2000	Italy	100	ALT 2x UL of nl, 3 times in last 6 mo, IFN monotherapy: IFN alpha-2b (3 mu tiw, for 4 mo) not w/i 6 mo of the study, detectable HCV in serum	Any antiviral agents w/i 6 mo of study, concomitant liver disease, thyroid dysfunction, pre-existing anemia, metabolic disorders (hemochromatosis, Wilson's disease, alph-1-antitrypsin deficiency), drug-induced liver disease, HIV+, immune suppression, presence of cirrhosis, hepatitis delta infection, HBV+, EtOH >40 g/d	To test the effectiveness of high dose IFN plus RBV vs. high dose IFN alone in previous IFN nonresponders.
Di Bisceglie, 2001	United States	124	Initial liver bx w/i 12 mos of rx, IFN monotherapy >=36 mu, detectable HCV in serum, positive HCV antibodies		To see if nonresponders to IFN alone would respond to a combination of IFN/RBV for either 24 or 48 wks
Ferenci, 2001a	Austria	157	HCV+, detectable HCV in serum, ALT 2x UL of nl, IFN monotherapy 5 mu tiw for 3 mo	Autoimmune thyroiditis, HBV+, depression, HIV+, EtOH >50 g/d, HBV surface antibodies, plts <100,000, uncontrolled DM, other liver diseases, WBC <3000, Hgb <12, cardiovascular or coronary artery disease	To study the efficacy of high-dose IFN alpha w/ or w/o RBV in IFN nonresponders.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Puoti, 2001	Italy	63	Detectable HCV in serum, age 18-60 yrs, ALT 1.5x nl, AFP, U/S, initial liver bx, IFN monotherapy, nonresponse to previous therapy	Depression, other psychiatric illness, pregnancy, adverse reaction to previous therapy, HIV+, HBV+, metabolic disorder, IDU, alcohol abuse, decompensated liver disease, cardiovascular comorbidity, other comorbidities: autoimmune, ascites, encephalopathy, uncontrolled diabetes, uncontrolled diabetes, unable to use OCPS, and neurologic, malignancy comorbidities: hemolytic anemia and thyroid disease, plts <100,000, WBC <3000, Hgb <12 for females and <13 for males	To assess efficacy of varying doses of IFN and RBV in previous nonresponders. Doses of IFN included 3 mu tiw, 5 mu tiw and 5 mu qd.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Saracco, 2001	Europe	594	HCV+, detectable HCV in serum, initial liver bx w/i prior 2 yrs, nonresponse to previous therapy, IFN monotherapy, age >18 and <65	Concomitant significant medical illness, IDU, HBV+, decompensated liver disease, relapse after previous therapy: >=1 course of IFN, pregnancy, depression, HIV+, cardiovascular comorbidity: ischemic cardiovascular disease, neurologic comorbidity: seizures, hematologic comorbidity: hemolytic anemia or hemophilia, abnl uric acid, obesity-induced liver disease, nonresponse to previous therapy: IFN and ribavirin combination therapy, other comorbidities: Wilson's disease, hemochromatosis, or autoimmune hepatitis, IFN + RBV, WBC <3000, neutrophil <500, Hgb <10 g/dl, plts <70,000, GI comorbidity, alpha-1antitrypsin deficiency	To assess if higher than standard doses of IFN given w/ RBV for prolonged periods of administration improved the rate of sustained response in previous IFN-alone nonresponders. The study compares the efficacy and safety of 3 mu and five mu of IFN plus 1000 mg daily RBV for either 6 or 12 mos
Shiffman, 2000a	United States	140	ALT, IFN monotherapy, pregnancy, nonresponse to previous therapy: IFN monotherapy	IFN monotherapy: max dose 6 mu IFN alpha-2a, OR max dose 9 mg IFN alphacon, OR max dose 3 mu IFN alpha-2b, any other type of liver disease, IDU, EtOH	To determine whether combination IFN/RBV was effective in tx of IFN monotherapy nonresponders. To determine subgroups who did not respond.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Tripi, 2000	Italy	72	Nonresponse to previous therapy: nonresponse to >= 2 courses of IFN (6 mu tiw, for 4 mo), detectable HCV in serum, ALT 2x UL of nl range, initial liver bx: CHC, IFN monotherapy 6 mo prior to study	HBV+, IDU, other illicit drug use, EtOH >50 g/d, Epstein-Barr virus, cytomegalovirus, immune suppression	To investigate the efficacy of IFN alone or IFN in combination w/ RBV in the retx of HCV+ nonresponders to IFN monotherapy
Studies of relapsers					
Chapman, 2001	New Zealand	32	ALT 1.5x nl, initial liver bx prior to initial tx, IFN monotherapy: 3 mu tiw for 6 mo ; relapsed w/i 6 mo of tx, contraception, detectable HCV in serum	Lactating, cardiovascular comorbidity, pregnancy	To compare the effect of high dose, long-term IFN therapy w/ shorter duration and lower dose IFN and RBV in IFN relapsers.
Di Marco, 2000	Italy	50	HCV+, initial liver bx, relapse after previous therapy, interferon monotherapy, age 18-65 yrs	Hemoglobinopathy, detectable HCV in serum, decompensated liver disease, HCC, immune suppression HIV+, HBV+, autoimmune disease, any antiviral therapy, uncontrolled diabetes, Hgb <12 for females and <13 for males, WBC <3000, plts <100,000, IFN, hematologic comorbidity: anemia, neutropenia, thrombocytopenia	To compare SVR in 6 vs. 12 mos of IFN alpha 2b 6 mu tiw and RBV 1-1.2 g/day in IFN relapsers. To examine the tolerability of higher doses of IFN + RBV. To identify predictors of response. To assess HCV viral dynamics.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Enriquez, 2000	Spain	120	HCV+, detectable HCV in serum, 6-mo duration of HCV+, el ALT for 6 mo, initial liver bx, relapse after previous therapy, nonresponse to previous therapy, 18-55 yrs	Cardiovascular comorbidity, IDU w/i the last year, presence of cirrhosis, decompensated liver disease, immune suppression, depression, HIV+, PT <50%, neurologic or GI comorbidity, renal insufficiency, poorly controlled DM, WBC <3000, neutrophil <1500, Hgb <12 for females and <13 for males, plts <100,000, other psychiatric illness	To see whether retx w/ IFN plus RBV for 24 or 48 wks would be beneficial in pts who relapsed or did not respond to previous IFN monotherapy
Studies of nonresponders and relapsers					
Bonkovsky, 2001	United States		Age >17, HCV+, detectable HCV in serum, prior tx w/ IFN w/ nonresponse or relapse, ALT 1.2x UL of nl, WBC >2,500, neutrophils >1,500, Hgb >12, plts >75,000	Decompensated liver disease, pregnancy, breastfeeding, or women of childbearing age refusing to use contraception, Immune suppression, depression or other psychiatric illness, cardiovascular comorbidity, alpha-1-antitrypsin deficiency, EtOH/non-EtOH steatohepatosis, hemochromatosis, Wilson's disease, severe renal disease, pulmonary disease, creatinine >2.0, transplant recipient, steroids/immunosuppression	To determine whether 600 mg RBV/day would prove as efficacious as 1000-1200 mg/day when combined w/ IFN (3 mu, tiw) for therapy of pts who relapsed or failed to respond to standard IFN

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Cavalletto, 2000	Italy	100	Nonresponse to previous therapy, HCV+, detectable HCV in serum, presence of fibrosis: CHC, presence of cirrhosis: CHC, age 18-60 yrs, relapse after previous therapy, peg-IFN alpha monotherapy >= 6 mo, initial liver bx w/i 12 mo of enrollment, initiation of therapy 12-24 mo after last tx w/alpha-IFN	Adverse reaction to previous therapy, allergy to IFN: intolerant to 1st course, pregnancy or "rejects contraception," HIV+, hematologic comorbidity: hemolytic disorder, HBV+, "recent" history of IDU, "recent" history of EtOH, decompensated liver disease: bx <1 yrs	To assess the effect of adding RBV to alpha-IFN for the retx of alpha-IFN relapsers and of previous alpha-IFN nonresponders.
Min, 2001	United States	154	IFN monotherapy for >3 mos, abnl ALT, initial liver bx showing CHC and/or cirrhosis, detectable HCV in serum	Women unwilling or unable to use contraceptives, IFN w/i 3 mos, IFN + RBV w/i 3 mos, immunomodulating or antiviral drugs w/i 3 mos, seizure disorder, other liver disease, cardiovascular comorbidity, severe psychiatric disorder, immune suppression, decompensated liver disease	To evaluate the efficacy of high dose IFN in combination w/ RBV in treating pts w/ CHC resistant to IFN monotherapy

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of interferon/amantadine combination therapy, with or without ribavirin					
Studies of nonresponders					
Brillanti, 2000	Italy		Nonresponse to previous therapy: defined as no HCV-RNA clearance and no ALT normalization; IFN alpha 3-6 mu, HCV+, absence of circulating anti-IFN antibodies, IFN monotherapy, 3-6 mu Ly or r IFN alpha for >=4 mo, initial liver bx: before first tx,el ALT for 6 mo, detectable HCV in serum	Comorbidities: GI, "other causes of chronic liver disease," pulmonary, renal, neurologic, seizure, diabetes, and cardiovascular, HBV+, immune suppression, depression, other psychiatric illness, HIV+, decompensated liver disease, plts <100,000 autoimmune hepatitis, alcoholic liver disease, WBC <3000, Hgb <12 in women and <13 in men	
Gaeta, 2001	Italy	40	Initial liver bx w/i prior 12 mo, ALT 1.5x UL of nl, nonresponsive to previous IFN alpha therapy, detectable HCV in serum, HCV+, HCV genotype 1b, age <60 yrs	Antihistamine, contraindication to IFN, renal disease, psychiatric illness, HIV+, decompensated liver disease, HBV+	To evaluate the efficacy and tolerability of high dose IFN plus amantadine for CHC pts who were nonresponders to a previous course of IFN

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Teuber, 2001	Germany	55	Age: 18-70, HCV+, detectable HCV in serum, ALT, initial liver bx, nonresponse to previous IFN, WBC >2,500, Plts >70,000	EtOH >50g, IDU or other illicit drug use w/i past year, HBV+, HIV+, decompensated liver disease, pregnancy and lactation, immune suppression, depression, other psychiatric illness, cardiovascular comorbidity, neurologic comorbidity, bleeding disorders, malignancy, autoimmune disorders, metabolic disease, renal disease, rheumatologic	To evaluate the efficacy, tolerability, and health-related quality of live of IFN alpha 2a plus amantadine in omparison w/ IFN alpha 2a plus placebo in previous nonresponders
Younossi, 2001	United States	118	Nonresponse to previous IFN monotherapy, initial liver bx, IFN monotherapy tiw for >=12 wk, HCV+	Other liver diseases, decompensated liver disease, immune suppression, severe depression, other severe psychiatric illness, HIV+, seizure disorders, DM, renal insufficiency, uncontrolled thyroid disease, plts <100,000, WBC <3000, Hgb <13 for males and <12 for females, active cardiovascular disease	To compare a 24 wk regimen of IFN alpha-2b plus RBV to IFN alpha-2b plus amantadine in nonresponders to previous IFN monotherapy

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of treatment outcomes in other subgroups					
Subgroup: Renal					
Campistol, 1999	Spain	36	Detectable HCV in serum, HCV+	HIV+, HBV+	Multicenter randomized trial assessing the efficacy and tolerance of IFN alpha-2b in tx of HCV induced chronic hepatitis in pts undergoing hemodialysis, w/ evaluation following renal transplant.
Subgroup: Race/ethnicity					
McHutchison, 2000	United States	1712			To evaluate racial differences in response to therapy in pts w/ CHC, and potential contributing factors that might account for such differences
Reddy, 1999	United States Canada	470			To retrospectively analyze data from the consensus IFN trial looking at outcomes in the specific tx arms (IFN-alpha-2b 3 mu tiw and alphacon IFN 9 mg) based on race.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Subgroup: Hemophiliacs					
Rumi, 1997	Italy	95	HCV+, detectable HCV in serum, ALT >= 2x nl on 3 occasions over 6 mo, HIV+	Peg-IFN monotherapy, HBV+, decompensated liver disease, HCC, EtOH >80 g/d, Peg-IFN + RBV, IFN, IFN + RBV, IFN monotherapy, steroid, WBC <3000, plts < 100,000, non-organ-specific autoantibodies, thyroid dysfunction	To evaluate the efficacy of long term (6 mo) IFN tx in hemophiliac pts
Subgroup: HBV/HCV coinfection					
Villa, 2001	Italy	30	Consecutively seen in clinic, ALT 2x nl for 6 mos, HBV+, HCV+	IFN tx, peg-IFN + RBV tx	To determine the outcome of medium to high doses of IFN therapy in pts w/ HBV-HCV.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of interferon in nonresponders/relapsers					
Bresci, 1996	Italy	150	ALT 2x UL of nl 3 times w/i 6 mo, 3 mu of rIFN, tiw, for 6 mo, nonresponse to previous therapy: detectable HCV in serum	Alpha-1-antitrypsin deficiency, Wilson's disease, hemochromatosis, drug-induced liver disease, immune suppression: autoimmune factors (+ANA, ASMA), presence of cirrhosis, hepatitis delta infection, HBV+, EtOH >40 g/d	To investigate the efficacy of different types of IFN and dosages in previous nonresponders to IFN tx (3 mu, tiw, for 6 mos)
Chemello, 1997	Italy	88	ALT 2.5x UL of nl, IFN monotherapy, detectable HCV in serum, relapse after previous therapy: 3 mu IFN alpha tiw for 6 mo or 3-6 mu IFN alpha tiw for 12 mo, nonresponse to previous therapy: 3 mu IFN alpha tiw for 6 mo or 3-6 mu IFN alpha tiw for 12 mo, age >18 and <55 yrs	Autoimmune disease, EtOH, HBV+, decompensated liver disease, HIV+, plts <100,000, metabolic disorders, ascites, varices, encephalopathy, WBC <3000, adverse reaction to previous therapy	Efficacy of retx w/ IFN in previous nonresponders and relapsers. The endpoints addressed were 1) predictors of virological and biochemical response and 2) influence of initial tx schedule on retx.
Gaeta, 1997	Italy	69	ALT 2x UL on 3 consecutive monthly samples, initial liver bx to test for HCV, LyIFN alpha for >= 4 mo, r IFN alpha for >=4 mo, nonresponse to previous therapy for >=4 mos w/ either r or LyIFN alpha, detectable HCV in serum	Abnl thyroid function, HIV+: tested for antibodies, decompensated liver disease, HBV+: screened for surface antigen HBsAg, immune suppression	To evaluate the efficacy and safety of leukocyte IFN-alpha in the retx of pts w/ chronic HCV who have failed to respond to therapy w/ either recombinant IFN-alpha or LyIFN-alpha.

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Heathcote, 1998	United States Canada	337	Plts 75 x 10^9, neutrophil >1.5 x 10^6, Hgb >10, ALT >48 x 2 consecutive values, consensus IFN 9 μγ tiw for 24/52 mo, consensus IFN 3 μγ tiw for 24/52 mo, IFN monotherapy 3 mu tiw for 24/52 mo	Seizure disorder and currently taking medication, thyroid disease in which nl thyroid function was not attainable, neurologic comorbidity, HIV+, depression, decompensated liver disease, IDU, EtOH	To determine the safety and efficacy of retx of CHC w/ consensus IFN for 24 wks vs. 48 wks at higher doses (15 μg) in nonresponders and relapsed pts.
Kagawa, 1998	Japan	62	ALT el persistently for >= 6 mo, initial liver bx: active CHC, detectable HCV in serum	HCC, hepatitis delta infection, HBV+	To evaluate the effect of higher doses of IFN in initial nonresponders. To evaluate early virologic response as a predictor of sustained response.
Payen, 1998	France	247	Abnl ALT for 6 mo, initial liver bx IFN monotherapy: 3 mu IFN, tiw for 6 mo, HCV+, detectable HCV in serum	Adverse reaction to previous therapy: grade 3 or 4 by WHO classification, HBV+, presence of cirrhosis, age <18 yrs, HIV+, Fe deposition in liver, women of childbearing age not using contraceptives, severe associated disease, pregnancy	To compare the efficacy of IFN alpha2b regimens in pts w/ CHC who relapsed after an initial 6 mo IFN tx

Evidence Table 13: Overall summary of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Poynard, 1999	France	58	ALT 1.5x nl in last 6 mo, IFN monotherapy: >= 3 mu tiw, for 24-48 wk, detectable HCV in serum, relapse after previous therapy, liver bx with CHC w/o cirrhosis, age 18-70 yrs	Neurologic comorbidity, EtOH 50 g/d, IDU, other illicit drug use, HBV+, hepatitis delta infection, immune suppression, depression, other psychiatric illness, cardiovascular comorbidity, plts <70,000, hematologic comorbidity, renal disease, pulmonary disease, thyroid disease, severe medical disorder, MRI HCC, AFP >100, neutrophil <2, HIV+	To compare the effect of high-dose, short duration (14 wks) IFN regimen in relapsers w/ standard 6 mo IFN regimen of 3 mu tiw.
Shiffman, 1999	United States	53	Nl alpha-antitrypsin, HCV+, detectable HCV in serum, nonresponse to previous therapy: IFN alfa-2b, histologic response to prior IFN tx, nl ceruloplasmin, nl antinuclear antibody, nl anti-smooth-muscle antibody, initial liver bx, ALT el 6 mo, WBC, IFN monotherapy, nl hepatic Fe levels, plts >90,000	HIV+, active IDU, abnl Alb, abnl Bili, HBV+, immune suppression, chronic EtOH, abnl prothrombin, abnl AFT, pregnancy	To assess if continued maintenance of IFN prevents HCV progression in virologic nonresponders who achieved a histological response after an initial 6 mo IFN tx.

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of current treatment options in nonresponders/relapsers to prior therapy										
Studies of nonresponders										
Barbaro, 1999	RCT									
		IFN: beta IFN, 6 mu, 6 days/week,	100	33		HAI	S 2.3		178	
		12 wks		67.0		HAI	T 11.7			
									1b	45.00
									2a/c	43.00
									3a	12.00
		IFN: alpha-2b, 6 mu tiw, 12 wks	100	32		HAI	S 2.2		175	
		RBV: 1000-1200 mg qd, 12 wks		65.0		HAI	T 11.5			
									1b	43.00
									2a/c	44.00
									3a	13.00
Bresci, 2000	RCT									
		IFN: 6 mu tiw, 6 mos	50	52		HAI	S 2.0		149	
		RBV: 1000-1200 mg qd, 6 mos		56.0		Kno	A 10.3		7	
									1	78.00
		IFN: 6 mu, bid, 6 mos	50	48		HAI	S 2.2		150	
				52.0		Kno	A 9.7		8	

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									1	74.00
Di Bisceglie, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	63	43		Sch		A0 20.6	90	
		RBV: 1000-1200 mg qd, 24 wks		69.8		Sch		A1 30.2		
				C: 96.8		Sch		A2 25.4	1	74.60
						Sch		A3 23.8	2	19.05
									3	6.35
		IFN: alpha-2b, 3 mu tiw, 48 wks	61	46		Sch		A0 18.0	100	
		RBV: 1000-1200 mg qd, 48 wks		57.4		Sch		A1 21.3		
				C: 98.3		Sch		A2 41.0	1	86.89
						Sch		A3 19.7	2	9.84
									3	3.28

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Ferenci, 2001a	RCT									
		IFN (initial): alpha-2b, 5 mu tiw, 3 mos	76	71.1				S3, A2 55.3 S4, A3 21.1	65.4	
		IFN (maintenance): alpha-2b, 10 mu, tiw, 3 mos							1a	15.79
									1a/b	2.63
									1b	68.42
									3	6.58
									4	6.58
		IFN (initial): alpha-2b, 5 mu tiw, 3 mos	81	70.4				S3, A2 63.0 S4, A3 17.3	69.8	
		IFN (maintenance): alpha-2b, 10 mu, tiw, 3 mos							1a	22.22
		RBV: 1000-2000 mg qd, 6 mos							1a/b	2.47
									1b	62.96
									3	6.17
									4	6.17

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Puoti, 2001									
		IFN: alpha-2b, 3 mu tiw, 24 wks	21						
		RBV: 1000-1200 mg qd, 24 wks		85.7					12
									1 71.43
									2 19.05
									3 4.76
									4 4.76
		IFN: alpha-2b, 5 mu tiw, 24 wks	21						
		RBV: 1000-1200 mg qd, 24 wks		81.0					10
									1 71.43
									2 23.81
									3 4.76
									4 4.76
		IFN: alpha-2b, 5 mu, qd, 24 wks	21						
		RBV: 1000-1200 mg qd, 24 wks		81.0					15
									1 61.90
									2 9.52
									3 14.29
									4 14.29

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Saracco, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 12 mos	139	46	12	ISH	A 2.6			
		RBV: 1000 mg qd, 12 mos		66.2		ISH	S 6.2			
									1	66.91
									2	16.55
									3	9.35
									4	7.19
		IFN: alpha-2b, 5 mu tiw, 12 mos	162	44	9	ISH	A 2.5			
		RBV: 1000 mg qd, 12 mos		74.7		ISH	S 6.4			
									1	60.49
									2	19.14
									3	13.58
									4	6.79
		IFN: alpha-2b, 3 mu tiw, 6 mos	142	46	15	ISH	A 2.8			
		RBV: 1000 mg qd, 6 mos		76.8		ISH	S 6.2			
									1	67.61
									2	14.79
									3	14.08
									4	3.52
		IFN: alpha-2b, 5 mu tiw, 6 mos	151	45	7	ISH	A 2.6			
		RBV: 1000 mg qd, 6 mos		78.1		ISH	S 6.0			
									1	68.87
									2	13.25
									3	11.26
									4	6.62

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
.									
Shiffman, 2000a	RCT								
		IFN (initial): alpha-2b, 5 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu, tiw, 3 mos	48	44.5 60.4 C: 50, B: 50	21	Kno	7.3		1 89.58
		IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu, tiw, 3 mos RBV: 1000-1200 mg, Divided dose, twice daily, 9 mos	42	43.6 69.0 C: 69.0, B: 30.9	19	Kno	7		1 88.10
		IFN: alpha-2b, 5 mu tiw, 6 mos RBV: 1000-1200 mg, Divided dose, twice daily, 9 mos	50	42.9 66.0 C: 64, B: 36	14	Kno	6.4		1 90.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Tripi, 2000	RCT									
		IFN: Leukocyte IFN alpha, 6	24	46.2		HAI	A 1.3		184.5	
		mu tiw, 6 mos		50.0		HAI	S 3.4			
									1a	12.50
									1b	66.67
									2a	12.50
									2a and b	4.17
									2b	4.17
		IFN: Leukocyte IFN alpha, 6	48	49.4		HAI	A 2.1		168.8	
		mu tiw, 6 mos		75.0		HAI	S 4.8			
		RBV: 1200 mg qd, 6 mos							1a	4.17
									1b	70.83
									2a	10.42
									2a and b	2.08
									2b	12.50
Studies of relapsers										
Chapman, 2001	RCT									
		IFN (initial): alpha-2a, 6 mu tiw, 6 mos		16 37 56.3						
		IFN (maintenance): alpha-2a, 3 mu, tiw, 6 mos							1	75.00
									2	25.00
		IFN: alpha-2a, 3 mu tiw, 6 mos	16	38						
		RBV: 1000 mg qd, 3 mos		62.5						
									1	37.50

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
									2	62.50
Di Marco, 2000	RCT									
		IFN: alpha-2b, 6 mu tiw, 6 mos	25	46.1	12	Met		A1, A2 64.0		
		RBV: 1000-1200 mg, bid, 6 mos		68.0		Met		A3 36.0		
						Met		S1-S3 88.0	1b	76.00
						Met		S4 12.0	other	24.00
		IFN: alpha-2b, 6 mu tiw, 12 mos	25	45.6	16	Met		A1-A2 72.0		
		RBV: 1000-1200 mg, bid, 12 mos		84.0		Met		A3 28.0		
						Met		S1-S3 84.0	1b	40.00
						Met		S4 16.0	other	28.00
Enriquez, 2000	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	58	40.22						
		RBV: 1000-1200 mg qd, 24 wks		79.3						
									1	82.76
									non-1	15.52
		IFN: alpha-2b, 3 mu tiw, 48 wks	62	39.87						
		RBV: 1000-1200 mg qd, 48 wks		77.4						
									1	80.65
									non-1	17.74

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of nonresponders and relapsers										
Bonkovsky, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	35	44						
		RBV: 600 mg, 400 mg A.M./200 mg P.M., 24 wks		68.6 C: 91.4, B: 0, A: 0, O: 8.57					1 non-1 not specified	68.57 28.57 2.86
		IFN: alpha-2b, 3 mu tiw, 24 wks	34	44						
		RBV: 1000-1200 mg qd, 24 wks		61.8 C: 97.0, B: 2.94, A: 0, O: 0					1 non-1 not specified	70.59 26.47 2.94
Cavalletto, 2000	RCT									
		IFN (initial): natural IFN, 6 mu tiw, 2 mos	50	38 60.0		ISH ISH	A 3.0 S 8.9			
		IFN (maintenance): natural IFN, 3 mu tiw, 6 mos				ISH ISH		3-4 22.0 6 12.0	1 2 3	56.00 20.00 24.00
		IFN (initial): natural IFN, 6 mu tiw, 2 mos	50	40 94.0		ISH ISH	A 3.1 S 9.6			
		IFN (maintenance): natural IFN, 3 mu tiw, 6 mos RBV: 1000-1200 mg qd, 6 mos				ISH ISH		3-4 28.0 6 12.0	1 2 3	68.00 20.00 12.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Min, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 12 mos	81	47						
		RBV: 1000-1200 mg, bid, 12 mos		69.1 C: 77.7, B: 6.17, O: 16.0					1 non-1	87.65 12.35
		IFN: alpha-2b, 5 mu tiw, 12 mos	73	47.2						
		RBV: 1000-1200 mg, bid, 12 mos		74.0 C: 80.8, B: 8.21, O: 10.9					1 non-1	83.56 17.81

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of interferon/amantadine combination therapy, with or without ribavirin										
Studies of nonresponders										
Brillanti, 2000	RCT									
		Amantidine:	20	47						
		IFN: alpha-2b, 5 mu tiw, 12 mos		65.0						
		RBV: 800 - 1000 mg qd, 12 mos							1	55.00
									2	30.00
									3	10.00
									4	5.00
		Amantidine: 200 mg qd, 12 mos	40	49						
		IFN: alpha-2b, 5 mu tiw, 12 mos		67.5						
		RBV: 800 - 1000 mg qd, 12 mos							1	57.50
									2	27.50
									3	7.50
									4	7.50

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Gaeta, 2001	RCT									
		Amanitidine (initial): 100 mg, bid, 4 wks Amanitidine (maintenance): 100 mg, bid, 5 mos IFN (initial): alpha-2a, 4.5 mu, qd, 4 wks IFN (maintenance): alpha-2a, 6 mu, tiw, 5 mos	21	44.7 66.7	5	Kno Sch	S 5.0 A 1.5		1b	100.00
		IFN (initial): alpha-2a, 4.5 mu, qd, 4 wks IFN (maintenance): alpha-2a, 6 mu, tiw, 5 mos	19	48.4 63.2	11	Kno Sch	S 5.5 A 1.5		1b	100.00
Teuber, 2001	RCT									
		Amantidine: 100 mg, bid, 48 wks IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 6 mu, tiw, 24 wks	26	47.7 73.1					73 10.9 1 non-1	 84.62 15.38
		Amantidine: Placebo IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 6 mu,	29	45.7 41.4					64 14.9 1 non-1	 93.10 6.90

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		tiw, 24 wks								
Younossi, 2001	RCT									
		IFN: alpha-2b, 3 mu tiw, 24 wks	59	46.1	17	HAI	8.1			
		RBV: 800 mg qd, 24 wks		62.7 C: 79.6, B: 18.6, O: 1.69					1a/b other	83.05 13.56
		Amantidine: 200 mg qd, 24 wks	59	45.6	17	HAI	7.1			
		IFN: alpha-2b, 3 mu tiw, 24 wks		61.0 C: 72.8, B: 10.1, O: 10.1					1a/b other	71.19 25.42

Studies of treatment outcomes in other subgroups

Subgroup: Renal

Campistol, 1999	RCT									
		IFN: alpha-2b, 3 mu tiw, 6 mos	19	42 47.4						
		IFN: None	17	48 58.8						

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Subgroup: Race/ethnicity										
McHutchison, 2000	RCT									
		IFN (210 pts): alpha-2b, 3 mu tiw, 24 wks	1460	43 65.1		HAI Kno	7.1 S 1.5		17	
		IFN (461 pts): alpha-2b, 3 mu tiw, 24 wks				Kno Kno		S3 1.1 S4 0.2	1 non- 1	65.06 34.94
		IFN (464 pts): alpha-2b, 3 mu tiw, 48 wks								
		IFN (465 pts): alpha-2b, 3 mu tiw, 48 wks								
		RBV (461 pts): 1000/1200 mg qd, 24 wks								
		RBV (464 pts): 1000/1200 mg qd, 48 wks								

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (12 pts): alpha-2b, 3 mu tiw, 24 wks IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks IFN (15 pts): alpha-2b, 3 mu tiw, 24 wks RBV (13 pts): 1000/1200 mg qd, 48 wks RBV (15 pts): 1000/1200 mg qd, 24 wks	53	46 67.9		HAI Kno Kno Kno	7.8 S 1.7	 S3 47.2 S4 11.3	18 1 non-1	 96.23 3.77
		IFN (1 pts): alpha-2b, 3 mu tiw, 24 wks IFN (13 pts): alpha-2b, 3 mu tiw, 24 wks IFN (6 pts): alpha-2b, 3 mu tiw, 48 wks IFN (7 pts): alpha-2b, 3 mu tiw, 48 wks RBV (13 pts): 1000/1200 mg qd, 24 wks RBV (7 pts): 1000/1200 mg qd, 48 wks	27	45 81.5		Kno Kno	S 1.5	 S4 40.7	21 1 non-1	 59.26 40.74

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (12 pts): alpha-2b, 3 mu tiw, 48 wks	32	45 75.0		HAI HAI	7.9	40.6	21	
		IFN (5 pts): alpha-2b, 3 mu tiw, 48 wks				Kno Kno	S3	6.2	1 non- 1	78.13 21.88
		IFN (7 pts): alpha-2b, 3 mu tiw, 24 wks				Kno	S4	88		
		IFN (8 pts): alpha-2b, 3 mu tiw, 24 wks								
		RBV (12 pts): 1000/1200 mg qd, 48 wks								
		RBV (8 pts): 1000/1200 mg qd, 24 wks								
Reddy, 1999	RCT									
		IFN (Caucasians): alpha-2a, 3 mu or alphacon1, 9 mu tiw, 24 wks	380	42 73.9		HAI	7	S4 3.16	132	
									1	2.11
									1a	37.89
									1b	26.05
									2a	3.95
									2b	12.11
									3	3.95
									other/mixed	2.89

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (African Americans): alpha-2a, 3 mu or alphacon1, 9 mu tiw, 24 wks	40	43 62.5		HAI	6	S4 12.5	116	
									1	2.50
									1a	52.50
									1b	32.50
									2a	10.00
									2b	2.50
									3	0.00
									other/mixed	0.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
		IFN (Hispanics): alpha-2a, 3 mu or alphacon1, 9 mu tiw, 24 wks	40	45 70.0		HAI	8	S4 50.0	118	
									1	2.50
									1a	40.00
									1b	25.00
									2a	2.50
									2b	12.50
									3	10.00
									other/mixed	7.50
		IFN (Asians): alpha-2a, 3 mu or alphacon1, 9 mu tiw, 24 wks	10	50 70.0		HAI	8	S4 80.0	117	
									1	0.00
									1a	20.00
									1b	20.00
									2a	20.00
									2b	30.00
									3	0.00
									other/mixed	10.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Subgroup: Hemophiliacs										
Rumi, 1997	RCT									
		IFN: alpha-2b, 3 mu tiw, 6 mos	45	33						
									1a	57.78
									1b	22.22
									2	6.67
									3	24.44
		IFN: None	50	34						
									1a	38.00
									1b	18.00
									2	18.00
									3	28.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Subgroup: HBV/HCV coinfection										
Villa, 2001	RTnc									
		IFN: 6 mu tiw, 6 mos	14	34		HAI	A 1.9			
				71.4		HAI	S 11.6			
									1a	7.14
									1b	78.57
									2a	14.29
		IFN: 9 mu tiw, 6 mos	16	33		HAI	A 1.7			
				75.0		HAI	S 11.9			
									1a	31.25
									1b	43.75
									2a	25.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of interferon in nonresponders/relapsers									
Bresci, 1996	RCT								
		IFN: alpha-2b, 3 mu tiw, 6 mos	30	46 56.7				S3, A2 70.7	120 8
		IFN: alpha-2b, 6 mu tiw, 6 mos	30	50 66.7				S3, A2 76.7	140 9
		IFN: alphacon1, 3 mu tiw, 6 mos	30	49 53.3				S3, A2 80.0	138 7
		IFN: natural IFN, 3 mu tiw, 6 mos	30	47 60.0				S3, A2 73.3	136 9
		IFN: None	30	48 56.7				S3, A2 76.7	146 8

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Chemello, 1997	RCT									
		IFN: 3-6 mu tiw, 6-12 mos	26	26 88.5						
									1	88.46
									2	88.46
									3	0.00
		IFN: 3-6 mu tiw, 6-12 mos	66	46 72.7						
									1	57.58
									2	34.85
									3	7.58
Gaeta, 1997	RCT									
		IFN (initial): Leukocyte IFN, 3 - 6 mu tiw, 6 mos	44	51.02 61.4		HAI		11.4		
		IFN (maintenance): Leukocyte IFN, 3 - 6 mu tiw, 6 mos							1a	13.64
									1b	34.09
									2a	11.36
									3 or 4	4.55
		IFN (initial): Recombinant or lymphoblastoid IFN alpha, 3 - 6 mu, tiw, 12 mos	25	47.2 64.0		HAI		24		
									1a	8.00
									1b	64.00
									2a	4.00
									3 or 4	4.00

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Heathcote, 1998	RCT									
		IFN (Relapsers): alphacon1, 15 µg, tiw, 24 wks	167	44.7 74.3					1	70.06
		IFN (Nonresponders): alphacon1, 15 µg, tiw, 24 wks	167	44.7 74.3					1	70.06
		IFN (Relapsers): alphacon1, 15 µg, tiw, 48 wks	170	44.3 75.9					1	74.12
		IFN (Nonresponders): alphacon1, 15 µg, tiw, 48 wks	170	44.3 75.9					1	74.12

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Kagawa, 1998	RCT								
		Early responders IFN (initial): alphacon1, 6 mu, qd, 4 wks Early responders IFN (maintenance): alphacon1, 6 mu tiw, 22 wks	30						
		IFN (initial): alphacon1, 6 mu, qd, 4 wks IFN (maintenance): alphacon1, 6 mu, tiw, 22 wks	16						
		IFN (initial): alphacon1, 6 mu, qd, 4 wks IFN (maintenance): alphacon1, 6 mu, tiw, 18 wks	16						

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Payen, 1998	RCT									
		IFN: alpha-2b, 3 mu tiw, 6 mos	75	45.6		HAI	7.2			
				92.0					8.83	
				C: 98.6					1	5.33
									1a	10.67
									1b	28.00
									2	13.33
									3	16.00
									other	8.00
		IFN: alpha-2b, 3 mu tiw, 12 mos	91	44.1		HAI	7.6			
				71.4					9.47	
				C: 100					1	3.30
									1a	3.30
									1b	29.67
									2	15.38
									3	23.08
									other	5.49
		IFN: alpha-2b, 10 mu tiw, 6 mos	81	42.1		HAI	8			
				70.4					9.08	
				C: 100					1	2.47
									1a	3.70
									1b	33.33
									2	9.88
									3	28.40
									other	6.17

Evidence Table 14: Characteristics of patients in randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Poynard, 1999									
		IFN: alpha-2b, 3 mu tiw, 24 wks	29	38 62.1					2.6 2.92 1 48.28 2/3 37.93 4 13.79
		IFN (initial): alpha-2b, 10 mu, 6 days a week, 2 wks IFN (maintenance): alpha-2b, 10 mu, tiw, 12 wks		29 39 62.1					3.17 1 51.72 2/3 37.93 4 6.90
Shiffman, 1999	RCT								
		IFN: None	27	48.8 51.9 C: 85.1, O: 14.8	22	Kno Kno	A 14.8 S 3.4		
		IFN: alpha-2b, 5 mu tiw, 24 mos	26	47.8 57.7 C: 88.4, O: 11.5	27	Kno Kno	A 7.7 S 1.8		

Evidence Table 15: Methodologic quality of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of current treatment options in nonresponders/relapsers to prior therapy							
Studies of nonresponders							
Barbaro, 1999	100	83	50	80	100	0	83
Bresci, 2000	50	67	50	75	50	0	58
Di Bisceglie, 2001	75	67	50	85	67	50	69
Ferenci, 2001a	63	17	50	70	38	0	47
Puoti, 2001	75	50	50	85	100	50	72
Saracco, 2001	88	83	100	70	88	0	86
Shiffman, 2000a	100	100	100	60	83	50	89
Tripi, 2000	63	58	50	85	38	50	59
Studies of relapsers							
Chapman, 2001	38	50	50	65	17	50	44
Di Marco, 2000	88	67	50	80	100	0	77
Enriquez, 2000	75	33	50	80	100	0	68
Studies of nonresponders and relapsers							
Bonkovsky, 2001	88	83	100	80	50	100	80
Cavalletto, 2000	100	67	50	90	100	50	81

Evidence Table 15: Methodologic quality of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Min, 2001	100	50	75	80	83	50	78
Studies of interferon/amantadine combination therapy, with or without ribavirin							
Studies of nonresponders							
Brillanti, 2000	100	67	100	75	100	50	88
Gaeta, 2001	50	67	100	70	0	0	57
Teuber, 2001	75	92	75	85	83	0	82
Younossi, 2001	63	100	100	80	100	100	89
Studies of treatment outcomes in other subgroups							
Subgroup: Renal							
Campistol, 1999	33	67	75	65	100	0	68
Subgroup: Race/ethnicity							
McHutchison, 2000	25	33	50	40	88	50	47
Reddy, 1999	38	75	75	80	63	50	66
Subgroup: Hemophiliacs							
Rumi, 1997	75	58	100	90	75	0	80
Subgroup: HBV/HCV coinfection							
Villa, 2001	88	83	75	35	67	100	70

Evidence Table 15: Methodologic quality of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of interferon in nonresponders/relapsers							
Bresci, 1996	88	50	50	70	67	0	65
Chemello, 1997	88	58	75	30	63	50	63
Gaeta, 1997	50	50	100	80	50	50	66
Heathcote, 1998	50	67	100	80	67	0	73
Kagawa, 1998	50	17	100	75	67	50	62
Payen, 1998	75	83	50	85	83	50	75
Poynard, 1999	63	83	75	65	83	50	74
Shiffman, 1999	63	67	50	75	83	50	68

Evidence Table 15: Methodologic quality of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 6 points. This included whether assignment of patients to study groups was randomized (2 points); whether groups had any differences in key patient characteristics (2 points); and whether clinicians, patients, and outcome assessors were blinded (2 points).

[c] ***Description of Therapy/Management***: The total maximum score was 4 points. This included sufficiently detailed description of the treatment regimen (2 points); and description of other treatments or tests given to subjects (2 points).

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 8 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); whether adjustment of potential confounders were multi-variate or stratified analyses and coding of confounders (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of current treatment options in nonresponders/relapsers to prior therapy								
Studies of nonresponders								
Barbaro, 1999	A IFN: beta IFN, 6 mu, 6 days/wk, 12 wks			17		65*[a]	2	24
10 mos.	B IFN: alpha-2b, 6 mu tiw, 12 wks			12		35*[a]	3	7
	RBV: 1000-1200 mg qd, 12 wks							
Bresci, 2000	A IFN: 6 mu tiw, 6 mos	20	14	38*[c]	8[c]		24	
12 mos.	RBV: 1000-1200 mg qd, 6 mos							
	B IFN: 6 mu, bid, 6 mos	16	15	12*[c]	6[c]			
Di Bisceglie, 2001	A IFN: alpha-2b, 3 mu tiw, 2 mos	69	38	49	41		17	17
6 mos.	RBV: 1000-1200 mg qd, 2 mos							
	B IFN: alpha-2b, 3 mu tiw, 4 mos	64	47	36	36		26	23
	RBV: 1000-1200 mg qd, 4 mos							
Ferenci, 2001a	A IFN (initial): alpha-2b, 5 mu tiw, 3 mos	26*	1.3	11*	1.3		22	
6 mos.	IFN (maintenance): alpha-2b, 10 mu tiw, 3 mos							
	B IFN (initial): alpha-2b, 5 mu tiw, 3 mos	43*	8.6	31*	8.6		21	
	IFN (maintenance): alpha-2b, 10 mu tiw, 3 mos							
	RBV: 1000-2000 ml, qd, 6 mos							

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Puoti, 2001	A IFN: alpha-2b, 3 mu tiw, 24 wks	52	5	52	5*†			38
6 mos.	RBV: 1000-1200 mg qd, 24 wks							
	B IFN: alpha-2b, 5 mu tiw, 24 wks	52	10	52	10*			38
	RBV: 1000-1200 mg qd, 24 wks							
	C IFN: alpha-2b, 5 mu, qd, 24 wks	70	38	70	38			43
	RBV: 1000-1200 mg qd, 24 wks							
Saracco, 2001	A IFN: alpha-2b, 3 mu tiw, 12 mos	47	16 §	25 §	15		12	
6 mos.	RBV: 1000 mg qd, 12 mos							
	B IFN: alpha-2b, 5 mu tiw, 12 mos	55*	30 R	42 R	23*		14	
	RBV: 1000 mg qd, 12 mos							
	C IFN: alpha-2b, 3 mu tiw, 6 mos	37*	14 §	22 §	11*		12	
	RBV: 1000 mg qd, 6 mos							
	D IFN: alpha-2b, 5 mu tiw, 6 mos	49*	17	26 §	16		13	
	RBV: 1000 mg qd, 6 mos							

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Shiffman, 2000a 6 mos.	A IFN (initial): alpha-2b, 5 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu tiw, 3 mos	6.3	0	0	0		21	
	B IFN (initial): alpha-2b, 3 mu tiw, 3 mos IFN (maintenance): alpha-2b, 5 mu tiw, 3 mos RBV: 1000-1200 mg, divided dose, bid, 9 mos	74	38	26	14		16.7	
	C IFN: alpha-2b, 5 mu tiw, 6 mos RBV: 1000-1200 mg, divided dose, bid, 9 mos	72	30	30	12		20	
Tripi, 2000 6 mos.	A IFN: alpha, 6 mu tiw, 6 mos	25	0	4.2*	0			
	B IFN: alpha, 6 mu tiw, 6 mos RBV: 1200 mg qd, 6 mos	38	8.3	25*	6.3		6	
Studies of relapsers								
Chapman, 2001 6 mos.	A IFN (initial): alpha-2a, 6 mu tiw, 6 mos		44	63	50			25
	IFN (maintenance): alpha-2a, 3 mu tiw, 6 mos							19
	B IFN: alpha-2a, 3 mu tiw, 6 mos RBV: 1000 mg qd, 3 mos		50	69	50			

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Di Marco, 2000 6 mos.	A IFN: alpha-2b, 6 mu tiw, 6 mos RBV: 1000-1200 mg, bid, 6 mos				36*		12	
	B IFN: alpha-2b, 6 mu tiw, 12 mos RBV: 1000-1200 mg, bid, 12 mos				72*		16	
Enriquez, 2000 6 mos.	A IFN: alpha-2b, 3 mu tiw, 24 wks RBV: 1000-1200 mg qd, 24 wks			45	16*			5
	B IFN: alpha-2b, 3 mu tiw, 48 wks RBV: 1000-1200 mg qd, 48 wks			47	37*			3

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of both nonresponders and relapsers								
Bonkovsky, 2001	A IFN: alpha-2b, 3mu tiw, 24 wks RBV: 600 mg qd, 24 wks	57	31	46	34		11	
	B IFN: alpha-2b, 3 mu tiw, 24 wks RBV: 1000-1200 mg qd, 24 wks	53	26.5	53	35		9	
Cavalletto, 2000 6 mos.	A IFN (initial): natural IFN, 6 mu tiw, 2 mos IFN (maintenance): natural IFN, 3 mu tiw, 6 mos				10			
	B IFN (initial): natural IFN, 6 mu tiw, 2 mos IFN (maintenance): natural IFN, 3 mu tiw, 6 mos RBV: 1000-1200 mg qd, 6 mos				24			
Min, 2001 6 mos.	A IFN: alpha-2b, 2 mu tiw, 12 mos RBV: 1000-1200 mg, bid, 12 mos			28	14		12.3	
	B IFN: alpha-2b, 5 mu tiw, 12 mos RBV: 1000-1200 mg, bid, 12 mos			29	22		21.9	

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Studies of interferon combination therapy with amantadine, with or without ribavirin								
Studies of nonresponders								
Brillanti, 2000 6 mos.	A IFN: alpha-2b, 5 mu tiw, 12 mos RBV: 800 - 1000 mg qd, 12 mos	20*	10*	10*	5*		0	
	B Amantidine: 200 mg qd, 12 mos IFN: alpha-2b, 5 mu tiw, 12 mos RBV: 800 - 1000 mg qd, 12 mos	78*	58*	68*	48*		0	
Gaeta, 2001 6 mos.	A Amanitidine (initial): 100 mg, bid, 4 wks Amanitidine (maintenance): 100 mg, bid, 5 mos IFN (initial): alpha-2a, 4.5 mu, qd, 4 wks IFN (maintenance): alpha-2a, 6 mu tiw, 5 mos	29		0			4.8	
	B IFN (initial): alpha-2a, 4.5 mu, qd, 4 wks IFN (maintenance): alpha-2a, 6 mu tiw, 5 mos	16		0			16	

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Teuber, 2001	A Amantadine: 100 mg, bid, 48 wks IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 6 mu tiw, 24 wks	19	4	4	0			
	B Amantadine: Placebo IFN (initial): alpha-2a, 6 mu tiw, 24 wks IFN (maintenance): alpha-2a, 6 mu tiw, 24 wks	28	14	14	7			
Younossi, 2001 6 mos.	A IFN: alpha-2b, 3 mu tiw, 24 wks RBV: 800 mg qd, 24 wks	56.7	12.1	34.8	3.9		20	
	B Amantidine: 200 mg qd, 24 wks IFN: alpha-2b, 3 mu tiw, 24 wks	47.1	7.8	19.6	0		17	
Subgroup: Renal								
Campistol, 1999 24 mos.	A IFN: alpha-2b, 3 mu tiw, 6 mos			58	26		53	
	B IFN: None			6				

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Subgroup: Race/ethnicity								
McHutchison,2000	A IFN (210 pts): alpha-2b, 3 mu tiw, 24 wks				27*			
6 mos.	IFN (461 pts): alpha-2b, 3 mu tiw, 24 wks							
	IFN (464 pts): alpha-2b, 3 mu tiw, 48 wks							
	IFN (465 pts): alpha-2b, 3 mu tiw, 48 wks							
	RBV (461 pts): 1000-1200 mg qd, 24 wks							
	RBV (464 pts): 1000-1200 mg qd, 48 wks							
	B IFN (12 pts): alpha-2b, 3 mu tiw, 24 wks				11*			
	IFN (15 pts): alpha-2b, 3 mu tiw, 24 wks							
	IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks							
	IFN (13 pts): alpha-2b, 3 mu tiw, 48 wks							
	RBV (13 pts): 1000-1200 mg qd, 24 wks							
	RBV (7 pts): 1000-1200 mg qd, 48 wks							
	C IFN (1 pt): alpha-2b, 3 mu tiw, 24 wks				44			
	IFN (13 pts): alpha-2b, 3 mu tiw, 24 wks							
	IFN (6 pts): alpha-2b, 3 mu tiw, 48 wks							
	IFN (7 pts): alpha-2b, 3 mu tiw, 48 wks							
	RBV (13 pts): 1000-1200 mg qd, 24 wks							
	RBV (7 pts): 1000-1200 mg qd, 48 wks							
	D IFN (7 pts): alpha-2b, 3 mu tiw, 24 wks				16			
	IFN (8 pts): alpha-2b, 3 mu tiw, 24 wks							
	IFN (12 pts): alpha-2b, 3 mu tiw, 48 wks							
	IFN (5 pts): alpha-2b, 3 mu tiw, 48 wks							
	RBV (8 pts): 1000-1200 mg qd, 24 wks							
	RBV (12 pts): 1000-1200 mg qd, 48 wks							

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Reddy, 1999	A IFN (Caucasians): alpha, tiw, 24 wks	44*	22*	33*	12		4	16
6 mos.	B IFN (African Americans): alpha, tiw, 24 wks	12.5*	8*	5*	2.5		12	18
	C IFN (Hispanics): alpha, tiw, 24 wks	25	10	28	10		8	18
	D IFN (Asians): alpha, tiw, 24 wks	40	30	40	30		10	20
Subgroup: Hemophiliacs								
Rumi, 1997	A IFN: alpha-2b, 3 mu tiw, 6 mos		26[c]		13[c]			
12 mos.	B IFN: None		0[c]		0[c]			
Subgroup: HBV/HCV coinfection								
Villa, 2001	A IFN: 6 mu tiw, 6 mos	64		86				
	B IFN: 9 mu tiw, 6 mos	81		75				
Studies of interferon in nonresponders/relapsers								
Bresci, 1996	A IFN: alpha-2b, 3 mu tiw, 6 mos	16.7	7.7	7.7[c]	3.3[c]			
6 mos.	B IFN: alpha-2b, 6 mu tiw, 6 mos	30	10	16.7[c]	7.7[c]			
	C IFN: alphacon1, 3 mu tiw, 6 mos	20	7.7	10[c]	3.3[c]			
	D IFN: natural IFN, 3 mu tiw, 6 mos	23	7.7	10[c]	3.3[c]			
	E IFN: None	10	10	0[c]	0[c]			

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Chemello, 1997	A IFN: 3-6 mu tiw, 6-12 mos	8	0	0	0			
	B IFN: 3-6 mu tiw, 6-12 mos	42	20	23	20			
Gaeta, 1997	A IFN (initial): alpha, 3 - 6 mu tiw, 6 mos	30*	23*	14	6.8			
12 mos.	IFN (maintenance): alpha, 3 - 6 mu tiw, 6 mos							
	B IFN: alpha, 3 - 6 mu tiw, 12 mos	0*	0*	0	0			
Heathcote, 1998	A IFN (Relapsers): alphacon1, 15 ug, tiw, 24 wks	88	39	72	28			
6 mos.	B IFN (Nonresponders): alphacon1, 15 ug, tiw, 24 wks	26	12	19	5			
	C IFN (Relapsers): alphacon1, 15 ug, tiw, 48 wks	76	52	76	58			
	D IFN (Nonresponders): alphacon1, 15 ug, tiw, 48 wks	25	17	17	13			

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

Author, Year Follow-up	Study Groups	Biochemical Response ETR %	Biochemical Response SR %	Viral Response ETR %	Viral Response SR %	Histological Response %	Adverse Events Disc/Withdr %	Adverse Events Dose Red %
Kagawa, 1998	A Early responders IFN (initial): alphacon1, 6 mu, qd, 4 wks		67	80	63 [R]			
6 mos.	Early responders IFN (maintenance): alphacon1, 6 mu tiw, 22 wks							
	B IFN (initial): alphacon1, 6 mu, qd, 4 wks		13	25	6 [§]		12.5	
	IFN (maintenance): alphacon1, 6 mu tiw, 22 wks							
	C IFN (initial): alphacon1, 6 mu, qd, 4 wks		6	44	0 [§]		6.25	
	IFN (maintenance): alphacon1, 6 mu tiw, 18 wks							
Payen, 1998	A IFN: alpha-2b, 3 mu tiw, 6 mos	71	12 [§]	44 [§]	11 [§]	46[a]		14
6 mos.	B IFN: alpha-2b, 3 mu tiw, 12 mos	69	36 [R]	43 [§]	24 [R]	57[a]		38.5
	C IFN: alpha-2b, 10 mu tiw, 6 mos	84	19 [§]	60 [R]	14 [§]	38[a]		30.8
Poynard, 1999	A IFN: alpha-2b, 3 mu tiw, 24 wks	86	17	38	14	28*	21	
11 mos.	B IFN (initial): alpha-2b, 10 mu, 6 days a wk, 2 wks	79	6.9	28	0	6.9*	14	
	IFN (maintenance): alpha-2b, 10 mu tiw, 12 wks							
Shiffman, 1999	A IFN: Placebo	41		3.7		37*		
36 mos.	B IFN: alpha-2b, 5 mu tiw, 24 mos	62		23		62*		

Evidence Table 16: Results of randomized controlled trials of current treatment options for selected subgroups of patients with chronic hepatitis C (continued)

[a] Percentage based on a denominator different from the group N
[c] Complete response, defined as combined virological and biochemical response
* $p < 0.05$ for the pairwise comparison between two groups marked with this symbol
† $p < 0.05$ for the pairwise comparison between two groups marked with this symbol

[§] $p < 0.05$ for the comparison groups marked with this symbol and the group marked [R]
[R] Reference group for comparison

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Randomized controlled trials						
Bernardinello, 1999	Italy	61	Tertiary care	IFN monotherapy, presence of cirrhosis: >= 2 regenerative nodules on bx, presence of fibrosis: >= 2 regenerative nodules on bx, age 18-65 yrs	Plts <50,000, WBC <2000, Child's C, portal hypertension, renal dysfunction, thyroid disease, immune suppression, decompensated liver disease, EtOH >80 g/d	To find the short- and long-term effects of IFN tx in pts w/ CHC w/ a long-term follow-up of 5 yrs.
Chemello, 1999	Italy	157	Unclear	ALT 2x UL nl for 6 mo prior to randomization, initial liver bx showing chronic liver disease, detectable HCV in serum, age 18-60 yrs	Thyroid disease, active EtOH, IDU, pregnancy, immune suppression, other causes of liver disease, plts <100,000, portal hypertension, ascites, varices, IFN monotherapy, WBC <3000, hematologic comorbidity: cytopenia	A 5 yr followup of a RCT comparing daily and tiw human leukocyte IFN alpha induction in CHC, followed by 3 mu IFN alpha tiw for 3 mos
Nishiguchi, 2001	Japan	90	Tertiary care	Abnl ALT for >1 yr, presence of cirrhosis, detectable HCV in serum	Plts <50,000, liver disease of any other etiology, HIV+, immune suppression: excluded for autoimmune hepatitis, HCC, HBV+, EtOH	To assess Child-Pugh progression, mortality, and HCC at long-term followup of 8 yrs after IFN tx alpha in HCV infected cirrhotic pts.
Long-term outcomes of treatment						
Aizawa, 2000	Japan	153	Tertiary care	ALT 2xUL nl, initial liver bx, HCV+	HBV+	Long-term observation of pts w/ CHC to elucidate the incidence of HCC and the factors that predict HCC.

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Benvegnu, 1997	Italy	429	Tertiary care	Presence of cirrhosis, detectable HCV in serum, HCV+	Autoimmune or metabolic liver disease, HCC, HBV+, excessive EtOH	To investigate the relationship between HCV genotype and the natural course of HCV, its complications, and development of HCC in cirrhotic pts
Bruno, 1997	Milan, Italy	163	Tertiary care	Presence of cirrhosis, HCV+, presence of fibrosis	IFN, HCC, Child's C, hemochromatosis, autoimmune hepatitis, sclerosing cholangitis, age >70 yrs, ALT >400	To prospectively follow a cohort of HCV pts w/ cirrhosis and evaluate if the HCV genotype impacts the development of HCC. In addition, the aim was to elicit other independent risk factors for HCC.
Fattovich, 1997	Italy, France, United Kingdom	329	Tertiary care	ALT 1.5x UL of nl for 6 mo, compensated cirrhosis, presence of cirrhosis, HCV+	Ascites, varices, encephalopathy, jaundice, any other potential cause of chronic liver disease, HCC, HBV+	To evaluate the role of IFN alpha in preventing the development of HCC or decompensation in a cohort of Caucasian pts w/ compensated cirrhosis.
Horiike, 1998	Japan	88	Unclear			To elucidate the effect of IFN therapy on the subsequent development of HCC in pts

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
						w/ CHC.
Ikeda, 2001	Japan	694	Tertiary care	Presence of cirrhosis, detectable HCV in serum, HCV+	Aggressive CHC, subacute hepatitis, HIV+	To elucidate whether IFN suppresses the rate of carcinogenesis in pts w/ HCV cirrhosis; To show the role of IFN in cancer presentation in liver cirrhosis type C. 1) To what extent could IFN decrease the carcinogenesis rate from HCV-related cirrhosis. 2) To explore the effective tx by using IFN therapy in prevention.
Inoue, 2000	Japan	923	Tertiary care	Positive HCV antibodies	Presence of cirrhosis, HBV+	To evaluate whether IFN reduces the incidence of HCC
Shibata, 1998	Japan	242	Tertiary care	AFP <2x nl, HCV+	Inadequate liver samples for histological assessment, presence of cirrhosis, presence of fibrosis, HCC, hepatitis A or HBV+	To determine if irregular regeneration of hepatocytes is a risk factor for HCC in pts w/ chronic hepatitis or cirrhosis of the liver caused by the HCV.

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Shindo, 2001	Japan	250	Community based	ALT 1.5x UL of nl for 6 mo, CHC on initial liver bx, detectable HCV in serum, HCV+	Refusal to take IFN, other forms of liver disease, presence of cirrhosis, HBV+, EtOH	To study the impact of long-term biochemical response to IFN in pts who did not have serum viral response, and to determine their clinical characteristics and long-term outcomes of cirrhosis and HCC.
Tanaka, 2000	Japan	726	Tertiary care	HCV+: 1st or 2nd generation ELISA, reside in Osaka Prefecture at time of dx of HCV	HBV+ at initial dx of HCV	To study the effects of IFN on long-term outcome of pts w/ CHC namely on incidence of HCC.
Toyoda, 2001	Japan	291	Community based	All Pts treated w/varied doses but only nonresponders were included, relapse after previous therapy, detectable HCV in serum, HCV+	Presence of cirrhosis, presence of fibrosis, HBV+	To evaluate the effects of dose and duration of IFN tx on rates of HCC in pts w/ non-sustained response to tx. The pts are non-cirrhotics.
Yabuuchi, 2000	Japan	419	Tertiary care	Initial liver bx	Serious illness, immune suppression, pregnancy, HBV+	To determine the characteristics of pts w/ CHC showing long-term normal-ization in ALT levels but not viral eradication. Also, the study investigated the incidence of HCC in these pts

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Yatsuhashi, 2000	Japan	186	Tertiary care	ALT el for 6 mos, initial liver bx showing CHC, detectable HCV in serum, positive HCV	AFP >400, U/S if evidence of HCC, HCC, presence of cirrhosis, presence of fibrosis, HBV+, daily EtOH >80 g/d for 5 yrs	To measure the natural history outcome in incidence of HCC of HCV in 186 individuals.
Long-term studies of natural history						
Barrett, 2001	Ireland	155	Community based	Detectable HCV in serum, HCV+	Mode of transmission: anti-D immunoglobulin in 1997, HCV genotype 1b, female	To study the natural history of HCV in a cohort of women w/ either chronic infection or spontaneous self-limited infection. Histology, symptomatology, psychosocial impact, and extrahepatic manifestations of HCV, and HLA class II associations evaluated.
Benhamou, 2001	France		Tertiary care	HCV+, detectable HCV in serum, presence of fibrosis/cirrhosis, HIV+, antiretroviral therapy for HIV	HBV+, immune suppression, doubtful compliance with antiretroviral therapy	To analyze the impact of different retroviral agents, including protease inhibitor therapy on HCV related liver fibrosis in HIV/HCV coinfected pts

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Chiaramonte, 1999	Italy	259	Tertiary care	Presence of cirrhosis, HBV+, HCV+	Wilson's disease, hemochromatosis, alcoholic liver disease, <12-mo f/u, immune suppression, HCC, decompensated liver disease	To prospectively assess the incidence of HCC in pts w/ HBV, HCV, or both w/ Child's Grade A viral cirrhosis
Cottone, 1994	Italy	147	Unclear	Age > 40 yrs, Child's A cirrhosis		To determine the risk of HCC in Child's A cirrhosis, whether 6 mos screening interval is adequate, and determine the role of AFP in screening
Forns, 2001	Spain	116	Unclear	ALT el for 6 mos, histopathologic dx of HCV	Negative anti-HCV during f/u, Wilson's disease, autoimmune hepatitis, anti-smooth muscle antibody 1:100, antinuclear antibody 1:100, decompensated liver disease, HBV+, EtOH >40 g/d	To analyze the long-term outcome of a large cohort of Spanish pts w/ CHC followed for more than 20 yrs to identify risk factors associated w/ progression of the disease
Furusyo, 2000	Japan		Community based	ALT, plt count, AST, GGT, Serum HA, serum type IV collagen	Current IFN, anti-retroviral therapy for HIV, lamivudine for HBV	To evaluate the liver damage of hemodialysis pts w/ HCV viremia through ALT and markers of hepatic fibrogenesis

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Gentilini, 1997	Italy	405	Unclear	Abdominal U/S, presence of cirrhosis, initial liver bx, prothrombin, upper GI endoscopy, ALT, plts, Bili, Alb, GGT	EtOH, pulmonary or metabolic disorder, HBV+, decompensated liver disease: portal hypertension, renal insufficiency	To examine the natural history of HBV and HCV in cirrhotics w/o portal hypertension
Harris, 2002	United Kingdom	1400	Community based		Dates of counseling not clear, transfused after blood tested for HCV, not flagged in NHS central register, any other exposure to blood products, IDU	To determine the clinical course of HCV infection in the first decade of infection in a group of pts who acquired their infections on a known date
Hayashi, 2000	Japan	274	Community based	ALT nl, AFP yearly 1994-1998, U/S yearly 1994-1998, HCV+, HCV genotype	HBV+	To clarify the mechanism of liver damage induced by HCV and whether it is related to HCC
Ikeda, 1993	Japan	795	Unclear	Presence of fibrosis/cirrhosis	HCC, idiopathic portal hypertension, Budd-Chiari syndrome, subacute hepatitis, chronic aggressive hepatitis w/ severe bridging necrosis, types of cirrhosis other than viral or alcoholic	To examine the incidence of HCC and explore risk factors for HCC in pts w/ cirrhosis, focusing on the difference between HCV and HBV

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Kliem, 1996	Germany	162	Tertiary care	Seen on 4-12 occasions/y, immune suppression: kidney transplant, HCV+	HCC, HBV+	To determine the impact of CHC on morbidity and mortality after kidney transplantation.
Kobayashi, 1996	Japan	136	Tertiary care	Histological assessment: examination >= 5 yrs after initial examination, abnl ALT 3 times in 6 mos prior to tx, age 18-60 yrs	Therapy: antiviral or immunosuppressive agents during f/u, complications that would affect prognosis, HIV+ HBV+, EtOH >80 g/d	To assess if the long-term histological outcome differs between HCV genotypes 1 and 2
Kobayashi, 2000	Japan	61	Unclear	Initial liver bx, IFN monotherapy for 6 mos, positive HCV antibodies		To assess the correlation between serial changes in ALT levels and histological outcome 5 yrs after tx of pts w/ CHC w/ IFN for 6 mos.
Lesens, 1999	Canada		Tertiary care	Detectable HCV in serum		To determine if HCV behaves like an opportunistic infection in which progressive liver failure is the primary manifestation in HCV/HIV coinfected pts
Matsumura, 2000	Japan	527	Tertiary care	Detectable HCV in serum, positive HCV antibodies	Nl ALT, immune suppression, HBV+	To study the progression of HCV in 527 pts as compared by genotypes

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
Meijer, 1999	Netherlands	45	Tertiary care	Detectable HCV in serum	Other liver disease, HIV+, HBV+	To elucidate the natural history of HCV in HIV negative pts w/ coagulation disorders.
Murakami, 1999	Japan	357	Tertiary care	Transfusion, ALT abnl >6 mos, no history of antiviral therapy, HCV+, detectable HCV in serum	Autoimmune hepatitis, multiple transfusion, HBV+, tattoo, GI comorbidity: primary biliary cirrhosis, IDU, metabolic liver disease, drug-induced hepatitis, IFN monotherapy, no history of EtOH >= 80 g/d for >= 3 yrs	To identify factors related to the development of cirrhosis and HCC in pts w/ HCV and w/ a history of transfusion.
Persico, 2000	Italy	37	Tertiary care	ALT persistently nl >=3 times during the year, initial liver bx, no signs or symptoms of chronic liver disease, HCV+	Decompensated liver disease, presence of fibrosis, HBV+, IDU	Prospectively evaluate progression of disease in a group of HCV+ pts w/ persistently nl ALT levels.
Punyagupta, 1999	Thailand	63	Tertiary care			To assess long-term outcomes (5-15 yrs) of HCV pts in Thailand
Rodger, 1999	Australia	105	Tertiary care		No obtainable medical record, <16 yrs	To evaluate rates of HCC, cirrhosis and death in a cohort of HCV+ pts after 25

Evidence Table 17: Overall summary of long-term outcomes of chronic hepatitis C (continued)

Author, Year	Location	N	Cohort Source	Inclusion Criteria	Exclusion Criteria	Study Aims
						yrs.
Rostaing, 1996	France	31	Tertiary care	Azathioprine, CSA, renal transplant, duration of HCV+ <10 yrs, HCV+		To determine whether immune suppression for renal transplant affects liver histology in pts w/ CHC
Takano, 1995	Japan	351	Tertiary care	Histological dx of CPH or CAH, initial liver bx, AFP w/i nl range, reside w/i 1 hr commute for > 5 yrs and had already been followed >= 5 years	Presence of fibrosis/cirrhosis, decompensated liver disease, HCC at time of initial bx, concurrent HCV & HBV	To compare the incidence of HCC in pts w/ CHC vs. chronic HBV
Thomas, 2000	United States	1667	Community based	HCV+, IDU, age >17 yrs	HIV+	To assess the natural history and frequency of end stage liver disease and viral clearance in a cohort of persons infected w/ HCV secondary to intravenous drugs.
Yano, 1996	Japan	70	Unclear	Initial liver bx, HCV+	Any previous therapy, immune suppression, presence of cirrhosis, HBV+, habitual heavy EtOH	To study the pathological evolution of chronic HCV hepatitis over time

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Randomized controlled trials										
Bernardinello, 1999	RCT									
		IFN (initial): beta IFN, 6 mu tiw, 6 mos	38	56 50						
		IFN (maintenance): beta IFN, 3 mu, tiw, 6 mos							1	76.32
									2	23.68
									3	0.00
		IFN (initial): None	23	58						
		IFN (maintenance):		61						
									1	69.57
									2	26.09
									3	4.35

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Chemello, 1999	RCT									
		IFN (maintenance): 3 mu tiw, 6	108	48				S1-S2 25.9	242	
		mos		58				S3 49.1	9.92	
								S4 17.6	1	48.15
									2	24.07
									3	13.89
									undetermined	6.48
		IFN (initial): 3 mu, qd, 3 mos	49	19				S1-S2 20.4	204	
		IFN (maintenance): 3 mu tiw, 3 mos		73				S3 67.3	9.83	
								S4 12.2	1	59.18
									2	20.41
									3	10.20
									undetermined	10.20
Nishiguchi, 2001	RCT									
		IFN (maintenance): Usual care	45	57.3		HAI	T 11.8		100	
				51						
									1	0.00
									2	73.33
									3	17.78
									4	8.89
		IFN (maintenance): 6 mu tiw, 24 wks	45	54.7		HAI	T11.7		117	
				62						
									1	2.22
									2	77.78
									3	13.33
									4	6.67

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Long-term outcomes of treatment									
Aizawa, 2000	CohR								
			153	48.3 75		Des Des Des Des Des Des Des Des		A1 42.5 A1-A2 8 6.3 A2-A3 5 7.5 A3 13.7 S1 22.9 S2 29.4 S3 24.8 S4 22.9	
Benvegnu, 1997	Coh?								
			62	57.3 29				S4, A3 1 4.5	
			194	57 15				S4, A3 4 5.2	
			133	60.2 11				S4, A3 3 1.0	
			34	1 3				S4, A3 7.9	
			6	55 50				S4, A3 1.4	

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Bruno, 1997	CohP									
		IFN (initial): IFN-alpha; Only	163	57.8						
		82/163 patients elected to go through treatment, 6 mu tiw, 6 mos		50						
		IFN (maintenance): IFN-alpha; Only patients who responded to the initial 6 mo regimen went through the maintenance phase, 3 mu tiw, 6 mos							1a 1b 2a/c 3a mixed not specified	0.61 61.96 29.45 1.23 1.84 4.91
Fattovich, 1997	CohR									
		IFN (maintenance):	193	57						
			136	53						

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Horiike, 1998	CohR									
			33	48.3		HAI		S1 81.8		
				64		HAI		S2 9.1		
						HAI		S3 9.1	1	33.33
									1/2	9.09
									2	57.58
			55	48.7		HAI		S1 54.5		
				73		HAI		S2 16.4		
						HAI		S3 29.1	1	72.73
									1/2	3.64
									2	23.64
			61	45.7		HAI		S1 47.5		
				70		HAI		S2 29.5		
						HAI		S3 23.0	1	45.90
									1/2	0.00
									2	16.39

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Ikeda, 2001	CohR									
		IFN (maintenance): None	581	58					53	
				62						
									1	57.31
									2	14.29
									other	3.61
		IFN (maintenance): Usual care, 3-6 mu, <12 mos	88	51 75					71	
									1	46.59
									2	48.86
									other	0.00
		IFN (maintenance): Usual care, 3-6 mu, >/= 12 mos	25	25 72					62	
									1	76.00
									2	20.00
									other	4.00
Inoue, 2000	CohR									
		IFN (maintenance): Not specified	224							
				70						
		IFN (maintenance): No treatment	699							
				56						

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Shibata, 1998	CohP								
			179	52.6 61					
			63	54.1 60 A: 100					

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Shindo, 2001	CohR									
			67	48		HAI	A 1.5		137	
				46		HAI	S 8.4			
									1b	56.72
									non-1b	43.28
			26	55		HAI	S 8.3		106	
				77						
									1b	73.08
									non-1b	26.92
			70	46		HAI	A 1.5		127	
				76		HAI	S 7.5			
									1b	91.43
									non-1b	8.57
			87	54		HAI	A 1.5		166	
				54		HAI	S 10.0			
									1b	91.95
									non-1b	8.05
			89	51		HAI	A 1.6		97	
						HAI	A 2.3			
						HAI	S 7.5		1b	
									non-1b	

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Tanaka, 2000	CohR									
		IFN tx groups	134	52.2						
				70						
									1	58.96
									2	8.21
									not available	40.30
		Control	594	51.7						
				69						
									1	70.03
									2	23.74
									not available	6.23
Toyoda, 2001	CohR									
		IFN (initial): natural IFN, >500 mu,	183	49.9		HAI/Des		S0-S1 61.2		
				63		HAI/Des		S2 27.9		
						HAI/Des		S3 10.9	1b	68.31
									2a	23.50
									2b	7.10
									mixed	1.09
		IFN (initial): natural IFN, <500 mu,	108	51.6		HAI/Des		S0-S1 56.5		
				61		HAI/Des		S2 29.6		
						HAI/Des		S3 13.9	1b	74.07
									2a	20.37
									2b	5.56
									mixed	0.00

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Yabuuchi, 2000	CohR								
			126	50.8		HAI		S1 38.1	
				71		HAI		S2 33.3	
						HAI		S3/S4 28.6	
			49	52.6		HAI		S1 51.0	
				59		HAI		S2 30.6	
						HAI		S3/S4 18.4	
			244	53.8		HAI		S1 24.6	
				66		HAI		S2 32.0	
						HAI		S3/S4 43.4	
Yatsuhashi, 2000	CohP								
			186	46		HAI		A1 28.0	
				75		HAI		A2 47.8	
						HAI		A3 24.2	
						HAI		S0 29.0	
						HAI		S1 38.2	
						HAI		S2 19.9	
						HAI		S3 18.3	

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Long-term studies of natural history									
Barrett, 2001	CohP								
			87	45.7 0 O: 100		HAI HAI	A 4.1 S 1.1		23 1b 100.00
			68	45.8 0 O: 100		HAI HAI	A 2.1 S 0.2		23 1b 100.00
Benhamou, 2001	CohR								
			63	37.7 60					16.62 1 23.81
			77	36.3 100					14.05 1 33.77
Chiaramonte, 1999	CohP								
			66	44.8 76					
			166	55.5 52					
			27	48.8					

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
				81					
Cottone, 1994	CohP								
			147	58					
				55					
Forns, 2001	CohR								
			116	42.9					161
				59					
Furusyo, 2000	CohP								
			80						
									7.7
									1b 81.25
									2a 13.75
									2b 2.50
									undetermined 2.50
			153						
									3.4
			228						
									1b 88.60
									2a 9.65
									2b 1.75
Gentilini, 1997	CohP								
			405	54	100				

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
				58						
Harris, 2002	CohR									
			925	43.6 48 C: 84.6, O: 14.5	4					
			475	41.5 47 C: 68.4, O: 31.5						
Hayashi, 2000	CohP									
			102	37						
									1a	91.18
									2a	8.82
									2b	0.00
			92	58						
									1a	89.13
									2a	9.78
									2b	1.09
			80	71						
									1a	87.50
									2a	11.25
									2b	1.25

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Ikeda, 1993	CohP								
		IFN (initial):	795	53					
				71					
				A: 100					
Kliem, 1996	CohR								
			162	44.5					
				59					
Kobayashi, 1996	CohR								
			100	45.8		HAI	A 2.2		89
				68		HAI	S 8.0		
									1b 96.00
									other 1 4.00
			36	42.7		HAI	A 2.1		114
				78		HAI	S 8.1		
									2a 55.56
									2b 16.67
									other 2 27.78
Kobayashi, 2000	CohR								
		IFN (initial): 6-10 mu, qd, 4-8 wks	61						96
		IFN (maintenance): 6-10 mu tiw, 16-22 wks		77					
									1b 86.89
									other 13.11

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Lesens, 1999	CS								
			81						
			53						
Matsumura, 2000	CohR								
			245	45.9 64					
			143	51.6 58					
			45	55.1 49					
			39	55.6 59					
			55	62.1 67					

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Meijer, 1999	CohR								
			26	38					
									19
									1a 42.31
									1b 30.77
									2a 3.85
									2b 11.54
									3a 7.69
									unclassified 3.85
			12	35					
									19
									1a 33.33
									1b 33.33
									2a 16.67
									2b 8.33
									3a 8.33
									unclassified 0.00
			7	46					
									19
									1a 42.86
									1b 14.29
									2a 0.00
									2b 28.57
									3a 14.29
									unclassified 0.00

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Murakami, 1999	CohP									
			161	55.9 43						
									1b	68.94
									2a	24.22
									2b	6.83
			196	56.9 44						
									1b	69.39
									2a	25.00
									2b	5.61
Persico, 2000	CohP									
			37	40.8 54		ISH	S 8.0			
									1a	5.41
									1b	37.84
									2a	51.35
Punyagupta, 1999	CohR									
			63	54 A: 100				S1 47.6 S2 31.7 S3 11.1 S4 9.5		

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Rodger, 1999	CC									
			35	44 71						
			70	52 57						
Rostaing, 1996	CohR									
			31	48 68					13.3	
Takano, 1995	CohR									
			124	49.6 67						
			127	33.2 80						
Thomas, 2000	CohP									
			40							
									1a	65.00
									1b	32.50
			1627							
									1a	61.95
									1b	26.00
									other	11.99

Evidence Table 18: Characteristics of patients in studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Yano, 1996	CohR		70	44.6 86 A: 100					

Evidence Table 19: Methodologic quality of studies evaluating long-term outcomes of chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Randomized controlled trials							
Bernardinello, 1999	75	67	100	35	67	50	69
Chemello, 1999	75	83	75	95	83	50	82
Nishiguchi, 2001	100	83	100	80	88	50	90
Long-term outcomes of treatment							
Aizawa, 2000	63	0	50	50	88	0	50
Benvegnu, 1997	75	75	75	40	50	50	63
Bruno, 1997	100	38	100	88	63	50	78
Fattovich, 1997	63	50	0	95	50	50	52
Horiike, 1998	38	50	0	60	50	0	40
Ikeda, 2001	38	38	75	85	88	0	65
Inoue, 2000	75	25	0	88	63	50	50
Shibata, 1998	88	25	50	88	100	50	70
Shindo, 2001	83	--	100	80	63	0	81
Tanaka, 2000	88	25	100	75	100	100	78
Toyoda, 2001	75	100	75	80	100	50	86

Evidence Table 19: Methodologic quality of studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Yabuuchi, 2000	38	33	0	40	67	0	36
Yatsuhashi, 2000	50	50	50	50	67	0	53
Long-term studies of natural history							
Barrett, 2001	100	75	0	44	63	0	56
Benhamou, 2001	100	50	0	67	83	0	60
Chiaramonte, 1999	63	--	0	70	75	50	52
Cottone, 1994	50	0	0	30	100	0	36
Forns, 2001	88	--	--	94	100	50	94
Furusyo, 2000	63	0	100	50	50	0	53
Gentilini, 1997	75	0	0	80	50	50	41
Harris, 2002	100	50	0	100	100	100	70
Hayashi, 2000	100	75	--	44	67	0	71
Ikeda, 1993	88	0	25	55	100	0	54
Kliem, 1996	63	0	100	81	83	0	65
Kobayashi, 1996	88	100	--	100	83	100	93
Kobayashi, 2000	67	75	0	67	100	0	62
Lesens, 1999	38	17	0	94	63	50	42

Evidence Table 19: Methodologic quality of studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Matsumura, 2000	75	--	--	50	100	0	75
Meijer, 1999	88	50	--	63	75	0	69
Murakami, 1999	88	--	50	100	100	0	84
Persico, 2000	88	--	--	70	83	0	80
Punyagupta, 1999	25	--	0	67	0	0	23
Rodger, 1999	25	25	50	38	25	0	33
Rostaing, 1996	38	0	0	67	13	0	23
Takano, 1995	100	0	0	70	38	0	42
Thomas, 2000	75	--	0	85	67	50	57
Yano, 1996	88	--	--	100	100	0	96

Evidence Table 19: Methodologic quality of studies evaluating long-term outcomes of chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 6 points. This included whether assignment of patients to study groups was randomized (2 points); whether groups had any differences in key patient characteristics (2 points); and whether clinicians, patients, and outcome assessors were blinded (2 points).

[c] ***Description of Therapy/Management***: The total maximum score was 4 points. This included sufficiently detailed description of the treatment regimen (2 points); and description of other treatments or tests given to subjects (2 points).

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 8 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); whether adjustment of potential confounders were multi-variate or stratified analyses and coding of confounders (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 20: Results of studies evaluating long-term outcomes of patients with chronic hepatitis C

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Randomized controlled trials											
Bernardinello, 1999	A: 6 mu B IFN/tiw for 6 mos - 3 mu for 6 mos	5.0		5.3				9		24*	Probable death includes OTL
	B: No tx	5.0		4.3				4.4		35*	
Chemello, 1999	A: 3 mu IFN alpha tiw x 6 mos	6									SVR: @ 6 mos., 9% @ 72 mos., 9%
	B: 3 mu IFN alpha qd x 3 mos, then tiw for 3 mos	6									SVR: @ 6 mos., 12% @ 72 mos., 12%
Nishiguchi, 2001	A: Pts w/ HCV given symptomatic tx	8.2	38	73*		56*		58*			
	B: Pts w/ HCV given 6 mu IFN alpha, tiw for 24 wks	9.2	4	27*		29*		11*			

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Long-term outcomes of treatment											
Aizawa, 2000	A: IFN therapy	8.25	0	26	-		-				HCC predictors: increased age, heavy drinking, histologic staging
	B: No IFN therapy	8.25	12	45	-		-		-		
Benvegnu, 1997	A: IFN therapy	5.6		5.5							
	B: No IFN therapy	5.6		30.2							
Bruno, 1997	A: IFN therapy	5.7		0							Risk factors included genotype 1b age >60, males
	B: No IFN therapy	5.7		28							
Fattovich, 1997	A: Pts w/ HCV, treated w/ IFN alpha	4.8	4	4					8*		
	B: Untreated controls	5.3	11	12					29*		
Horiike, 1998	A: Complete responders to IFN	7.6	0	0*							Groups A v C and B v C are significant
	B: Nonresponders to IFN	7.6	1.5	2*							
	C: No IFN received	7.6	5	15*							

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Ikeda, 2001	A: No IFN	7.6	28.4	52.5			21	45.8			10 year rate for HCC
	B: Short-term IFN <12 mos	7.6	24.7	64.9			11	19.3			
	C: Long-term IFN >/= 12 mos	7.6	16.0	21.2			8	12			
Inoue, 2000	A: Pts treated w/ IFN	4.6	2.2*	2.2			0	2			Cox 69% decrease in HCC in patients receiving IFN
	B: Pts not treated w/ IFN	5.9	9.5*	14.4			15	12			
Shibata, 1998	A: Chronic hepatitis	3.5		7							Untreated cirrhotics 52% HCC treated noncirrhotics 6.29%
	B: Cirrhosis	3.5		52							

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Shindo M, 2001	A: Complete responders to tx (serum viral response and serum biochemical response)	8-11	3	0	8	8					
	B: Biochemical responders (nl ALT but no loss of virus)		3.9	0	8	8					
	C: Short-term responders (relapse of ALT)				8	8					
	D: Nonresponders				52	65.5					
	E: Control group				35	39					
Tanaka, 2000	A: Pts in IFN tx group w/ sustained response.	5.0	1.2	2			1				Risk of HCC in SR or TR vs controls=.16
	B: Pts in IFN tx group w/ transient response.	4.7	3.7	3			6				
	C: Pts who were nonresponders to IFN.	4.6	10	10			6				
	D: Control group - no IFN	5.6	14	13.1			7				
	E: Groups A, B, C			5.5			7				

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Toyoda, 2001	A: Pts who received >500 mu of IFN.	5		0							Results reported for both groups combined, no difference in HCC by duration, but significant by total dose.
	B: Pts who received <500 mu of IFN.	5		15							
Yabuuchi, 2000	A: Complete responders	4.9	2.3								Group A vs C and group B vs C are significant.
	B: HCV virus+ biochemical responders	5.2	2.0								
	C: Nonresponders	4.9	14.3								
Yatsuhashi, 2000	O: Natural history of HCV in 186 individuals		3.9	45		37					
Long-term studies of natural history											
Barrett, 2001	A: Polymerase chain reaction+ women w/ CHC	22.0		0.0		0.0					
	B: Polymerase chain reaction negative women w/ CHC			0.0		0.0					

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Benhamou, 2001	A: HIV/HCV coinfected pts treated w/ protease inhibitor				2	9			1.36*		
	B: HIV/HCV coinfected pts not treated w/ protease inhibitor				5	27			2.1*		
Chiaramonte, 1999	A: Pts+ for HBsAg	5.5	9	10							Risk factors: age >50, dual infection, male
	B: HCV+ Pts		20	21							
	C: Pts+ for both HBsAg and HCV		40	23							
Cottone, 1994	O: Overall		19								
Forns, 2001	O: Pts w/ noncirrhotic non-A, non-B hepatitis diagnosed at a tertiary hospital between 1971 and 1977	39	6	22	11						

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Furusyo, 2000	A: Hemodialysis pts w/ HCV+ RNA in serum	10	4								
	B: Hemodialysis pts w/ HCV- RNA in serum										
	C: Village residents with HCV viremia										
Gentilini, 1997	O: Pts w/ viral induced cirrhosis		8.6	9		19					
Harris, 2002	A: Transfusion recipients infected w/ HCV	11				1	13				Age, gender, alcohol increase mortality. HCV-RNA level, age >40, duration associated with liver disease.
	B: Transfusion recipients negative for HCV					2	9				
Hayashi, 2000	A: nl ALT levels	5		0*							
	B: Itermittenlty abnl ALT			4*							
	C: Aways abnl ALT			31							
Ikeda, 1993	O: Pts w/ cirrhosis	5.8		28		29					

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Kliem, 1996	O: Anit-HCV+ Pts	7.4						9			HBV increases risk of progressive deterioration.
Kobayashi, 1996	A: Pts infected w/ HCV genotype 1	9.4		29							More severe progression in patients w/ genotype 1 than genotype 2
	B: Pts infected w/ HCV genotype 2			6							
Kobayashi, 2000	O: Consecutive pts w/ CHC	5									
Lesens, 1999	A: HIV and HCV+ hemophiliacs	5					9	60			Rate of progressive liver disease: 27% Group A, 6% Group B
	B: HCV+ and HIV- hemophiliacs						0	21			
Matsumura, 2000	A: Pts w/ mild fibrosis	5							12		Overall rate for f1, f2, f3
	B: Pts w/ moderate fibrosis										
	C: Pts w/ severe fibrosis										

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
	D: Pts w/ cirrhosis										
	E: Pts w/ HCC										
Meijer, 1999	A: Nl liver/spleen by U/S	19									
	B: Nl liver, enlarged spleen w/ patent portal splenic veins										
	C: Abnl liver w/ patent portal/splenic veins										
Murakami, 1999	A: Pts analyzed for progression to cirrhosis.	5.0		12	21						As age at original transfusion inc., cumulative % HCC dec.
	B: Pts analyzed for progression to HCC.										
Persico, 2000	O: Asymptomatic HCV w/ persistently nl ALT levels	7.0				14					Cirrhosis in patients who did not have persistent nl ALT
Punyagupta, 1999	O: HCV positive patients	5-15		16	3						60% deceased at 10 years and 85% at 15 years.

Author, Year	Group Description	Avg Length of f/u (Yr)	HCC 5 yr Incidence %	Overall Incidence %	Cirrhosis 5 yr Incidence %	Overall Incidence %	HCV Overall Mortality %	All Cause Related Mortality %	Annual Fibrosis Progression %	Overall Rate of Decompensation %	Comments
Rodger, 1999	A: 35 anti-HCV+ individuals (followed up from a cohort of 238)			0	2						
	B: 70 anti-HCV- controls (followed up from a cohort of 1182)			0	1						
Rostaing, 1996	O: Renal transplant Pts given liver bx										
Takano, 1995	A: CHC pts				10.5						Patients with CHC more histologically advanced
	B: Chronic HBV pts			3.9							
Thomas, 2000	A: IDUs who are HCV w/ ESLD	8.8			7	2	25		2	98	Reported for all groups combined
	B: IDUs who are HCV w/o ESLD										
Yano, 1996	O: HCV+ Pts w/ chronic liver disease	8.8			50						

* denotes statistical significance for a comparison between groups ($p<0.05$)

Evidence Table 21: Overall summary of study addressing efficacy of screening tests for hepatocellular carcinoma to improve outcomes in patients with chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Solmi, 1996	Italy	2530	AFP, U/S, initial liver bx, chronic liver disease regardless of etiology (cirrhotics and noncirrhotics)	HCC	To evaluate the possibilities of diagnosis of HCC at an early stage through the use of serial U/S and AFP on a population at risk for HCC

Evidence Table 22: Characteristics of patients in study addressing efficacy of screening tests for hepatocellular carcinoma to improve outcomes in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Solmi, 1996	CohP								
		A: Chronic liver disease Pts w/o	360	52	71			S3, A2	29.4
		cancer followed in study center		76					
		B: Pts w/ liver cirrhosis or chronic	2170	56	70			S3, A2	29.9
		hepatitis followed in US clinics		65					

Evidence Table 23: Methodologic quality of study containing efficacy of screening tests for hepatocellular carcinoma to improve outcomes in patients with chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Solmi, 1996	100	50	100	65	33	0	70

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 6 points. This included whether assignment of patients to study groups was randomized (2 points); whether groups had any differences in key patient characteristics (2 points); and whether clinicians, patients, and outcome assessors were blinded (2 points).

[c] ***Description of Therapy/Management***: The total maximum score was 4 points. This included sufficiently detailed description of the screening tests (2 points); and description of other treatments or tests given to subjects (2 points).

[d] ***Outcomes and Followup:*** The total maximum score was 10 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); proportion of patients who withdrew from the study or were lost to followup (2 points); and sufficiency of the planned length of followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 8 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); whether adjustment of potential confounders were multi-variate or stratified analyses and coding of confounders (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 24: Results of study evaluating efficacy of screening tests for hepatocellular carcinoma to improve outcomes in patients with chronic hepatitis C

Article ID	Author, Year	Screening Groups	N	Mean Followup (months)	# Cases HCC	Unifocal at Diagnosis	Resectable at Diagnosis (≤3.0 cm)
2818	Solmi, 1996	A Chronic liver disease pts w/o cancer followed in study center	360	56	24	18	18
		B Pts w/ liver cirrhosis or chronic hepatitis followed in US clinics	2170	56	129	20	20

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of AFP (with or without other tests)					
Studies of HCV patients					
Prospective cohort studies					
Bruno, 1997	Italy	163	Presence of cirrhosis, HCV+, presence of fibrosis	IFN, HCC, Child's C, hemochromatosis, autoimmune hepatitis, sclerosing cholangitis, age >70 yrs, ALT >400	To prospectively follow a cohort of HCV pts w/ cirrhosis and evaluate if the HCV genotype impacts the development of HCC. In addition, the aim was to elicit other independent risk factors for HCC.
Tradati, 1998	Italy	385	Large pool clotting factor concentrates >= 10 yrs before start of study, ALT 1.5x UL of nl 3-6 mos apart		To assess the natural history of HCC in Italian hemophiliacs w/ el ALT To assess whether HCC screening (U/S and AFP) leads to early detection and improved chance of curative tx
Diagnostic Test Design					
Raedle, 1995	Germany	147	Detectable HCV in serum, ALT el	HIV+, other causes of cirrhosis or HCC	To determine the sensitivity and specificity of anti-p53 in screening for HCC in pts w/ CHC

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Studies of patients with HCV or HBV *Prospective cohort studies*					
Cottone, 1994	Italy	147	Age > 40 yrs, Child's A cirrhosis		To determine the risk of HCC in Child's A cirrhosis, whether 6 mos screening interval is adequate, and determine the role of AFP in screening
Ishii, 2000	Japan	734	HCC at time of entry or w/i 1 yr, presence of fibrosis: histological dx in Pts w/ CHC, agreed to >= 1-y f/u and had >= 6-mo f/u before entry, PIVKA-II, AFP, U/S if HCC was not detected		To determine if AFP and protein induced by vitamin K absence (PIVKA-II) measurements can improve detection of HCC in pts w/ chronic hepatitis.
Izzo, 1998	Italy	1125	Positive sera for HBV surface antigen in 3 separate measures at 3-mo intervals or positive sera for anti-HCV in 3 separate measures at 3-mo intervals, chronic HBV or CHC or both for >5 yrs	Positive previous dx of any type of malignancy, decompensated liver disease: Child's B or C cirrhosis, encephalopathy, bleeding GI varices, ascites	To determine the incidence of HCC (resectable HCC and survival rate) in pts w/ chronic HBV and HCV
Izzo, 1999	Italy	1520	HBsAg in 3 samples at 3-mo intervals or serum positive for anti-HCV virus in 3 samples at 3-mo intervals, chronic HBV or CHC infection or both for >= 5 yrs	Gastroesophageal varices, ascites, hepatic encephalopathy, bleeding, Child's B or C disease, positive history of any type of malignancy	To compare soluble IL-2 receptor to AFP as methods of screening for HCC in pts w/ chronic HBV or HCV. Also, to assess the usefulness of soluble IL-2 receptor as a marker of successful HCC tx and recurrence of disease.

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Larcos, 1998	Australia	232			To determine the incidence of HCC in pts w/ cirrhosis or chronic hepatitis and to assess cost and potential benefit of sonographic screening
Tong, 2001	United States	602	1 yr-f/u in clinic prior to study, presence of cirrhosis, HBV+ or HCV+	HCC	To determine whether AFP or U/S was more accurate in detecting HCC, and to elucidate problems encountered using these two modalities. Clinical outcomes of pts in whom HCC was detected are also evaluated.
Trevisani, 1995	Italy	475			To determine the prevalence of etiologic factors and clinical manifestations of HCC in pts w/ and w/o cirrhosis
Diagnostic Test Design					
Nomura, 1996	Japan	128		Obstructive jaundice	To assess the diagnostic values of new enzyme immunoassays for des-gamma-carboxy prothrombin (DCP) compared to AFP in small sized HCC

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Case control studies					
Sassa, 1999	Japan	195	Des-gamma-carboxy prothrombin, AFP		To investigate the effectiveness of high sensitivity des-gamma-carboxy prothrombin and Lens culinaris agglutinin A-reactive AFP screening tests in diagnosing small HCC.
Sato, 1993	Japan	361	Presence of cirrhosis, AFP >= 30 ng/mL		To determine the lectin reactivity of AFP in pts w/ cirrhosis who did and did not develop HCC
Tsai, 1994	China	404			To determine the frequency of raised AFP level among Chinese pts w/ HCC related to HBV and HCV
Tsai, 1995	Tiawan	256	Presence of cirrhosis, no previous therapy, serum samples collected		To evaluate the diagnostic efficacy of AFP and 4% PEG-CICs, and C1 q-CICs in detecting HCC in cirrhotic patients
Tsai, 1997	China	238	HCC group A, presence of cirrhosis: groups A and B	Previous treatment for cirrhosis or HCC, EtOH for HCC pts but not clear for control group	To evaluate the diagnostic efficacy of urinary transforming factor B-1 (TGF-B1) and AFP levels for detection of HCC in cirrhotic pts.

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Van Roey, 2000	Belgium	140	Initial liver bx, HCC	Non-HCC primary lesion of liver at dx or f/u	To study the characteristics of HCC pts w/ emphasis on the difference between cirrhotic HCC and noncirrhotic HCC pts
Cross-sectional studies					
Cedrone, 2000	Italy	350	ALT >2 x UL of nl	Pregnancy, autoimmune disorders, chronic alcohol abuse	To verify (in Western pts) w/ post-viral chronic liver disease, the utility of AFP for the detection of HCC, and the influence of HCV and HBV viral etiology on AFP levels in HCC.
Studies of other serological tests (without AFP)					
Studies of HCV patients					
Prospective cohort studies					
Kakumu, 1997	Japan	82			To understand the roles of sTNF-alpha, IL-10, and IL-15 in the pathogenesis of type C chronic liver disease using ELISA.
Studies of patients with HCV or HBV					
Cross-sectional studies					
Tsuzurahara, 1997	Japan	170	HBV+, detectable HCV in serum, HCV+		To determine whether MAGE-4 protein is detectable in sera of pts w/ HCC and other liver diseases

Evidence Table 25: Overall summary of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Location	N	Inclusion Criteria	Exclusion Criteria	Study Aims
Case control studies					
Nagai, 2001	Japan	129	ALT, AFP, initial liver bx, HCC (not an inclusion criteria in the controls), presence of cirrhosis, presence of fibrosis, HCV+		To assess if cytokeratin 19 fragment (CK19) will be increased in serum from pts w/ hepatoma.
Studies of imaging (without AFP)					
Studies of HCV patients					
Prospective cohort studies					
Kasahara, 1998	Japan	1022	ALT >= 2x UL of nl for >=6 mos, initial liver bx, positive HCV antibodies	<200 mu IFN, duration of f/u <12 mos, encephalopathy, ascites, varices, autoimmune liver disease, alcoholic liver disease, HCC w/i 1 yr of IFN therapy, HBV+	To evaluate the effect of IFN on HCC by assessing risk factors for carcinogenesis and incidence of HCC in pts w/ CHC treated w/ IFN.
Studies of patients with HCV or HBV					
Prospective cohort studies					
Colombo, 1991	Japan	447	Age > 36 yrs, Presence of fibrosis/cirrhosis, Childs A or B, willing to participate in follow-up visits	HCC	To assess the magnitude of risk, the natural history of disease, and the possibilities of detecting potentially resectable tumors.

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of AFP (with or without other tests)										
Studies of HCV patients										
Prospective cohort studies										
Bruno, 1997	CohP									
		O: All HCV+ cirrhotic pts attending an outpt clinic	163	57.8 50						
									1a	0.61
									1b	61.96
									2a/c	29.45
									3a	1.23
									mixed	1.84
									not specified	4.91
Tradati, 1998	CohP									
		O: Hemophiliacs treated w/ blood or plasma products w/ el aminotransferases	385	31 [m] 98	10				20	
Diagnostic Test Design										
Raedle, 1995	DTD									
		O: Pts w/ CHC	147	47.1 60						

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of patients with HCV or HBV *Prospective cohort studies*									
Cottone, 1994	CohP	O: Child's A cirrhosis pts receiving periodic screening by AFP and U/S of the liver	147	58 55					
Ishii, 2000	CohP	A: HBsAg+ Pts w/ cirrhosis	27						
		B: HCV+ Pts w/ chronic hepatitis	295						
		C: HCV+ Pts w/ cirrhosis	268						
		D: HBsAg+ Pts w/ cirrhosis, who were+ for HCV	4						
Izzo, 1998	CohP	O: 1125 Pts w/ HBV or HCV or HBV and C infection of >5 yrs	1125	56.1				S3, A2 28.9 S3, A2 71.1	 10.2
Izzo, 1999	CohP	O: 1520 Pts w/ HBV, HCV or HBV and HCV for >5 yrs	1520	56 61				S3, A2 69.9 S4, A3 30.1	 10.6

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Larcos, 1998	CohP	O: Pts w/ chronic hepatitis and/or cirrhosis	232	51 66 A: 20.6				S3 A2 5 1.3	
Tong, 2001	CohP	A: Pts w/ HBV infection	160	46 71 C: 13.7, B: 4.37, A: 78.7, O: 3.12					
		B: Pts w/ HCV infection	429	53 54 C: 55.9, B: 6.29, A: 17.7, O: 20.0					
		C: Pts w/ both HBV and HCV infections	13	49 77 C: 46.1, A: 46.1, O: 7.69					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Trevisani, 1995	CohR								
		A: HCC pts w/ cirrhosis	373	61.5 79					
		B: HCC pts w/o cirrhosis	102	58 61					
Diagnostic Test Design									
Nomura, 1996	DTD								
		A: HCC	27	74					
		B: Cirrhosis	69						
		C: Minimal or mild chronic hepatitis with no or mild fibrosis	17						
		D: Moderate or severe chronic hepatitis with moderate or severe fibrosis	15						

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Case control studies									
Sassa, 1999	CC								
		A: Cases: HCC <2 cm maximum diameter in Pts w/ CHC and cirrhosis	61	62 A: 100					
		B: Controls: Pts w/ chronic hepatitis or cirrhosis	134	A: 100					
Sato, 1993	CC								
		A: Cirrhosis caused by HCV or HBV w/ baseline AFP >/= 30 ng/mL and subsequent HCC	33	54 73					
		B: Cirrhosis caused by HCV or HBV w/ baseline AFP >/= 30 ng/mL w/o subsequent HCC	32	50 81					
Tsai, 1994	CC								
		A: HCC pts	177	59 85					
		B: Health community controls	177	85					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Tsai, 1995	CC								
		A: Cirrhotics w/ HCC	101	57 91					
		B: Sex-age matched controls w/ cirrhosis	101						
		C: Healthy volunteers	54	55 85					
Tsai, 1997	CC								
		A: Non-alcoholic cirrhotic HCC	94	58 [m] 81					
		B: Cirrhosis alone	94						
		C: Healthly controls: anti-HCV and anti-HBV negative	50	55 [m] 78					
Van Roey, 2000	CC								
		A: Noncirrhotics w/ HCC	56	50 61					36
		B: Cirrhotics w/ HCC	84	62 82					64

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Cross sectional studies									
Cedrone, 2000	XS								
		A: Pts w/ HCC and cirrhosis	74	65.5					
		B: Pts w/ cirrhosis	72	61.3					
		C: Pts w/ chronic hepatitis	197	53.7					
		D: Pts w/ nl liver at bx	7	54.5					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of other serological tests (without AFP)									
Studies of HCV patients									
Prospective cohort studies									
Kakumu, 1997	CohP								
		A: Asymptomatic HCV carriers w/ nl ALT for at least 1 yr	10	49 50					32
		B: Pts w/ chronic hepatitis and el ALT for at least 1 yr	28	54 71					111
		C: Pts+ for HCV-RNA w/ el ALT for at least 1 yr and cirrhosis	22	61 73					85
		D: Pts w/ HCC	11	66 82					78
		E: Healthy, HCV- controls, w/o a history of hepatitis and w/o liver disease	11	45 64					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of HCV or HBV patients *Cross sectional studies*									
Tsuzurahara, 1997	XS								
		A: Chronic HCV	70	51.2 49 A: 100					
		B: Chronic HCV w/ cirrhosis	55	61.5 44 A: 100					
		C: Chronic HCV w/ HCC	45	63.4 82 A: 100					
		D: Others							

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of patients with HCV or HBV *Case control studies*									
Nagai, 2001	CC								
		A: Pts w/ HCC	70	60 76 A: 100					
		B: Pts w/ CAH	14	53 64 A: 100					
		C: Pts w/ liver cirrhosis	45	58 67 A: 100					

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)	
Studies of imaging (without AFP)										
Studies of HCV patients										
Prospective cohort studies										
Kasahara, 1998	CohP									
		A: Sustained responders (6 mos following tx)	313	52.4 67		HAI	9			
									1	35.46
									2	34.82
									mixed	2.56
									unclassified	0.96
									untested	26.20
		B: Transient response	304	52.6 66		HAI	8.9			
									1	68.42
									2	10.53
									mixed	0.99
									unclassified	0.00
									untested	20.07
		C: Nonresponders	405	53.5 68		HAI	9.6			
									1	67.90
									2	9.63
									mixed	0.00
									unclassified	0.25
									untested	22.22

Evidence Table 26: Characteristics of patients in studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Study Design	Study Groups	N	Mean age % Male Race	% w/ Cirrhosis	Scoring System	Mean Activity (A) Fibrosis (S)	% w/ Score Activity (A) Fibrosis (S)	Mean ALT (U/L) Mean yrs w/ HCV HCV genotype (%)
Studies of patients with HCV or HBV *Prospective cohort studies*									
Colombo, 1991	CohP								
		A: (Overall) Italian pts with cirrhosis	447	55 69					
		B: detectable with HCC at enrollment	30	59 80					
		C: detectable with HCC over follow-up	29	58 79					

[m] Value given is a median

Evidence Table 27: Methodologic quality of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of AFP (with or without other tests)							
Studies of HCV patients							
Prospective cohort studies							
Bruno, 1997	100	50	50	83	67	50	70
Tradati, 1998	63	100	100	33	50	50	69
Diagnostic Test Design							
Raedle, 1995	75	50	100	0	100	0	65
Studies of patients with HCV or HBV							
Prospective cohort studies							
Cottone, 1994	50	50	100	13	100	0	63
Ishii, 2000	75	--	100	83	67	0	81
Izzo, 1998	75	0	100	25	50	50	50
Izzo, 1999	83	50	100	25	75	0	67
Larcos, 1998	25	50	100	100	25	0	60
Tong, 2001	63	0	100	50	67	0	56

Evidence Table 27: Methodologic quality of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Trevisani, 1995	88	50	50	0	100	50	58
Diagnostic Test Design							
Nomura, 1996	25	50	100	0	0	0	35
Case control studies							
Sassa, 1999	13	0	50	50	50	0	33
Sato, 1993	50	50	100	0	67	0	53
Tsai, 1994	88	50	50	67	100	50	71
Tsai, 1995	50	50	100	100	100	0	80
Tsai, 1997	63	50	50	50	100	0	63
Van Roey, 2000	38	50	50	100	75	0	63
Cross sectional studies							
Cedrone, 2000	88	50	100	50	100	0	78
Studies of other serological tests (without AFP)							
Studies of HCV patients							
Prospective cohort studies							
Kakumu, 1997	50	--	100	17	100	50	67

Evidence Table 27: Methodologic quality of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]
Studies of patients with HCV or HBV							
Cross sectional studies							
Tsuzurahara, 1997	25	50	50	100	100	50	65
Case control studies							
Nagai, 2001	38	0	50	100	67	0	51
Studies of imaging (without AFP)							
Studies of HCV patients							
Prospective cohort studies							
Kasahara, 1998	100	100	100	69	67	0	87
Studies of patients with HCV or HBV							
Prospective cohort studies							
Colombo, 1991	88	0	100	83	75	0	69

Evidence Table 27: Methodologic quality of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, Year	Representativeness[a]	Bias[b]	Description[c]	Outcomes[d]	Statistics[e]	Conflict[f]	Total[g]

[a] ***Representativeness***: The total maximum for this section was 8 points. This included setting and population described and start and end date specified (2 points); detailed description of inclusion and exclusion criteria or statement that all potential trainees enrolled (2 points); information about excluded or not-participating patients (2 points); and description of key patient characteristics at enrollment (2 points).

[b] ***Bias and Confounding***: The total maximum score was 2 points. This included whether there was an independent, blind comparison with a reference standard.

[c] ***Description of Therapy/Management***: The total maximum score was 2 points. This included sufficiently detailed description of the screening tests

[d] ***Outcomes and Followup:*** The total maximum score was 8 points. This included description of complications, side effects and adverse reactions (2 points); sufficient description of criteria for determining outcomes (2 points); reporting on the numbers and reasons for withdrawals from the study or losses to followup (2 points); and proportion of patients who withdrew from the study or were lost to followup (2 points).

[e] ***Statistical Quality and Interpretation***: The total maximum score was 6 points. This included whether magnitude of difference between groups and an index variability was stated (2 points); whether analyses and statistical tests were clearly identified (2 points); and appropriate handling of crossovers and/or dropouts in the analysis (2 points).

[f] ***Conflict of Interest***: The total maximum score was 2 points. This included whether the study reported the source of funding and the role played by the funding entity.

[g] ***Total Score*** is the mean of the percentage scores from the categories, Representativeness, Bias and Confounding, Description of Therapy/Management, Outcomes and Followup, and Statistical Quality and Interpretation.

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Studies of AFP (with or without other tests)							
Studies of HCV patients							
Cohort studies							
Bruno, 1997	163	CohP	AFP >20 ng/mL	27			
			AFP >400 ng/mL	4.5			
Tradati, 1992	385	CohP	AFP >11mg/mL	100			
			AFP >400 mg/mL	17			
Diagnostic Test Design							
Raedle, 1995	174	DTD	AFP >20 ng/mL	86	86		
			AFP >100 ng/mL	43	99		
			AFP >400 ng/mL	14			
			+anti-p53	43	100		
			AFP >20 ng/mL & +anti-p53	86	86		
			AFP >100 ng/mL & +anti-p53	71	99		

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Studies of patients with HCV or HBV							
Prospective cohort studies							
Cottone, 1994	147	CohP	AFP >50 ng/mL	36			
			AFP >400 ng/mL	0			
Ishii, 2000	734	CohP	AFP >= 20 ng/mL	61	78	6.5	98
			AFP >= 40 ng/mL	45			
			PIVKA-II >60 mA U/mL	41	91	16	97
			AFP >= 40ng/mL and PIVKA II >80 mAU/mL	66	85	15	98
Izzo, 1998	1125	CohP	AFP >10 ng/mL	75			
			U/S	87			
			U/S or AFP >10 ng/mL	100			

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Izzo, 1999	1520	CohP	AFP >10 ng/mL	80	95	81	94
			S-IL2R >850 U/mL	99	96	86	100
			U/S	66			
			CT/MRI	100			
Larcos, 1998	232	CohP	AFP >81 ng/mL	17		3%	
			U/S			24	
Tong, 2001	1204	CohP	AFP >13 ng/mL	59	91	11	99
			AFP >19 ng/mL	45	94	11	99
			AFP >21 ng/mL	41	94	11	99
			AFP >24 ng/mL	41	95	12	99
			U/S	100	98	78	100

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Trevisani, 1995	475	CohR	AFP>20 Solitary HCC	50			
			AFP>20 Massive HCC	50			
			AFP>20 Diffuse	70			
			AFP>20 Multimodular	70			
			AFP>40 Solitary	14			
			AFP>40 Massive	38			
			AFP>40 Diffuse	38			
			AFP>40 Multimodular	27			
Diagnostic Test Design							
Nomura, 1996	128	DTD	AFP >20	63			
			Conventional DCP	17			
			Overnight DCP	29			
			Avidin biotin complex DCP	33			

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Case control studies							
Sassa, 1999	195	CC	AFP >200 mg/mL	8	100		
			AFP >200 ng/mL and AFP L3 >10%	25	99	94	74
			AFP L3 >10%	23	99	93	74
			H-DCP >40 mAU/mL	45	99	93	80
			H-DCP > and AFP >200 ng/mL	47.5	99	94	81
			H-DCP > and AFP L3 >10%	54	98	92	83
Sato, 1993	361	CC	AFP >=30 ng/mL	68			
			AFP <30 ng/mL	86			
Tsai, 1994	404	CC	AFP >20 ng/mL	74	100		
			AFP >400 ng/mL	54			

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Tsai, 1995	256	CC	AFP >20 ng/mL	77			
			AFP >120 ng/mL	67			
			AFP >400 ng/mL	64			
			3% PEG circulating immune complexes	65			
			AFP >120 ng/mL + 3% PEG CIC	84	100		
			AFP >400 ng/mL + 3% PEG CIC	83	100		
Tsai, 1997			AFP >100 ng/mL	55	99	98	69
			AFP >400 ng/mL	48	100	100	66
			TGF B1>=50 mg/gCr	53	99	98	68
			TGF B1 >=50 or AFP >100 ng/mL	84	98	98	86
			TGF B1>=50 mg/gCr or AFP >400 ng/mL	80	99	99	83

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Van Roey, 2000	140	CC	AFP>20 ng/mL	62			
			AFP>50 ng/mL	55			
			AFP>400 ng/mL	43			
			U/S	51			
Cross sectional studies							
Cedrone, 2000			AFP >13 ng/mL	70	83	53	
			AFP >13 ng/mL in cirrhotic pts.	70	71	71	
			AFP >20 ng/mL	55	88	55	
			AFP >20 ng/mL in cirrhotic pts.	55	79	73	
			AFP >50 ng/mL	35	94	70	
			AFP >50 ng/mL in cirrhotic pts.	35	94	87	
Studies of other serological tests (without AFP)							
Studies of HCV Patients							
Prospective cohort studies							
Kakumu, 1997	80	CohP	IL10>5 pg/ml	63			
			IL15 >70 pg/ml	45			

Evidence Table 28: Results of studies addressing performance characteristics of screening tests for detecting hepatocellular carcinoma in patients with chronic hepatitis C (continued)

Author, year	N	Study Design	Test (cutoff)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Studies of HCV or HBV patients							
Cross sectional studies							
Tsuzurahara, 1997	170	XS	MAGE 4 >1.04 ng/mL	47	77	43	80
Case control studies							
Nagai, 2001	129	CC	CK >2.5 ng/mL	47	95	92	61
Studies of imaging (without AFP)							
Studies of HCV patients							
Prospective cohort studies							
Kasahara, 1998	1022	CohP	U/S and CT		96		
Studies of HCV or HBV patients							
Prospective cohort studies							
Colombo, 1991	447	CohP	U/S	49			
			U/S + CT	93			

Acronyms and Abbreviations

Abbreviation	Term
^	to the power of
+ANA	antinuclear antibody
IV-C7S	7S type IV collagen
A1	mild inflammation
A2	moderate inflammation
A3	marked inflammation
abnl	abnormal
AFP	alpha fetoprotein
Alb	albumin
ALT	alanine aminotransferase
AMA	against medical advice
ASMA	antismooth muscle antibody
AST	aspartate aminotransferase
beta-NAG	N-acetyl-beta-glucosaminidase
bid	twice a day
Bili	bilirubin
bx	biopsy
CA	carbohydrate antigen
CAH	chronic active hepatitis
CC	case control
CD4	CD4 count (cell type)
CEA	carcoembryonic antigen
CHC	chronic hepatitis C
CI	confidence interval
CohP	cohort prospective
CohR	cohort retrospective
CPH	chronic persistent hepatitis
Cr	creatinine
CS	case series
CSA	cyclosporine
CT	computerized tomography
D	day(s)
DM	diabetes mellitus
Des	Desmet
Disc/withdr	discontinued treatments or withdrew from study
Dose red	dose reduction
dx	diagnosis
el	elevated
ELISA	enzyme-linked immunosorbent assay
ETR	end of treatment response
f/u	follow-up
G	grade
g	gram(s)

GGT	gamma glutamyl transpeptidase
HA	hyaluronic acid
HbsAg	hepatitis B surface antigen
HAI	histological activity index
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
Hgb	hemoglobin
hr	hour(s)
IDU	intravenous drug user
IFN	interferon
Ig	immunoglobulin
IL	interleukin
ISH	Ishak
ITT	intention to treat
IV	intravenous
Kno	Knodell
L	liter(s)
LDH	lactate dehydrogenase
LL	lower limit
Ly IFN alpha	lymphoid interferon
MRI	magnetic resonance imaging
min	minute(s)
Met	Metavir
mL	milliliter(s)
MMP	matrix metalloproteinase
Mn-SOD	manganese superoxide dismutase
mo(s)	month(s)
MRI	magnetic resonance imaging
MU	million units
n/s	not specified
NASH	nonalcoholic steatohepatitis
ng	nanograms
nl	normal
NP	n-terminal polypeptide
NR	not reported
NS	not significant
OCPs	oral contraceptives
OLT	orthotopic liver transplant
PCHE	pseudocholinesterase
PCR	polymerase chain reaction
peg-IFN	pegylated interferon
P-III-P	Procollagen type III peptides
pts	patients
plts	platelets
PT	prothrombin time
PTT	partial thromboplastin time

qd	once a day
r IFN	recombinant IFN
r/o	rule out
RBV	ribavirin
RCT	randomized controlled trial
S	staging
S0	no fibrosis
S1, S2	mild (portal) fibrosis
S3	moderate (bridging) fibrosis
S4	severe fibrosis (cirrhosis)
SBR	sustained biochemical response
sec	second(s)
Sch	Scheuer
SR	sustained response
SVR	sustained virological response
tid	three times a day
TIMP	tissue inhibitor of metalloproteinase
tiw	three times a week
tx	treatment
U/S	ultrasound
ug	micrograms
UL	upper limit
w/	with
w/I	within
w/o	without
WBC	white blood cell
WHO	World Health Organization
wk	week(s)
XS	cross-sectional
yr(s)	year(s)

Appendix A. Reviewers

Expert Area and Organization	Name	Home Institution
Representatives of Professional Associations		
American Association for the Study of Liver Diseases (AASLD)	Henry C. Bodenheimer, Jr., MD	Mount Sinai School of Medicine
The American College of Physicians-American Society of Internal Medicine (ACP-ASIM)	Harold Fallon, MD	National Academy of Science
The American Academy of Pediatrics (AAP)	Samuel Kocoshis, MD	University of Cincinnati School of Medicine
Infectious Diseases Society of America (IDSA)	David Oldach, MD	University of Maryland School of Medicine
Other Clinical Experts		
Infectious diseases	John G. Bartlett	Johns Hopkins University School of Medicine
Infectious disease nursing	Sherilyn Brinkley-Laughton, MSN	Johns Hopkins University School of Nursing
Hepatology	Robert L Carithers Jr, MD	University of Washington, Seattle, WA
Internal medicine and infectious diseases	Lawrence Deyton, MD MSPH	US Department of Veteran Affairs
Adult hepatology	Lorna Dove, MD	Columbia University, New York
Clinical epidemiology and program policy	Roger Gibson, PhD, DVM, MPH	United States Air Force, Richmond, VA
Clinical epidemiology	Murray Krahn	University Health Network, Toronto, Canada
Hepatology	Mark C Mitchell, MD	Carolinas Medical Center
Pediatric hepatology	Kathleen Schwarz, MD	Johns Hopkins University, Baltimore, MD
Hepatology, hepatitis C, intravenous drug abuse and methadone	Diana Sylvestre, MD	University of California, San Francisco, CA
Methodologic Experts		
Developing best practice models for hepatitis C	Michael Chapko, PhD	Veterans Administration Health Services, Seattle, WA
Outcomes researcher and decision analyst	Mark Fendrick, MD	University of Michigan Schools of Medicine and Public Health, Ann Arbor, MI
Assessment of diagnostic technologies	Ben Littenberg, M.D.	University of Vermont
Pharmaceutical assessment	John Ticehurst	Department of Pathology, Johns Hopkins University

Expert Area and Organization	Name	Home Institution
Payor		
Division of medical items and devices, coverage and analysis group	John Whyte, MD MPH	Center for Medicare and Medicaid Services
Consumer Representatives		
Hep C Connection	Anne Jesse	Founding Director

Appendix B. Priority Journals for Handsearching

Priority Journal Titles	**Frequency**
AIDS	every three weeks
Annals of Internal Medicine	semi-monthly
British Medical Journal	weekly
Clinical Infectious Diseases	semi-monthly
Gastroentrology	monthly
Hepatology	monthly
Journal of Infectious Diseases	semi-monthly
Journal of the American Medical Association	weekly
Lancet	weekly
New England Journal of Medicine	weekly

Appendix C. Literature Search Strategy

PubMed Core Strategies

Key Questions 1a-1e

Name: Hepatitis C (Ques. 1a-1e)
Date and Time search last updated: 26-Sep-2001 12:59:03
Database: PubMed
Search: (hepatitis c, chronic[mh] OR hepatitis c[mh]) AND liver/pa AND (biopsy[mh] OR fibrosis[mh] OR liver function tests[mh]) NOT ("addresses"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "classical article"[Publication Type] OR "clinical conference"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "duplicate publication"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "historical article"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "letter"[Publication Type] OR "meeting report"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "overall"[Publication Type] OR "periodical index"[Publication Type])
Limits: Publication Date from 1996 to 2001, English, Human

Key Questions 2a-2c

Name: Hepatitis C (Ques. 2a-2c)
Date and Time search last updated: 26-Sep-2001 11:44:42
Database: PubMed
Search: ("treatment outcome"[MESH] OR "disease progression"[MESH] OR "disease free survival"[MESH] OR "Carcinoma, Hepatocellular"[MESH] OR pregnancy[MESH] OR demography[MESH] OR "ethnic groups"[MESH] OR "immunologic factors"[MESH] OR "immunologic diseases"[MESH] OR immunosuppression[MESH] OR "organ transplantation"[MESH] OR "drug therapy/adverse effects"[MESH] OR "antiviral agents/adverse effects"[MESH] OR "antiviral agents/therapeutic use"[MESH] OR "mental disorders"[MESH] OR prisoners[MESH] OR institutionalization[MESH] OR Comorbidity[MESH] OR "liver diseases"[MESH] OR "kidney diseases"[MESH] OR genotype[MESH] OR "Drug Therapy, Combination"[MESH]) AND "hepatitis c, chronic/therapy"[MESH] NOT ("addresses"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "classical article"[Publication Type] OR "clinical conference"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development

conference, nih"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "duplicate publication"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "historical article"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "letter"[Publication Type] OR "meeting report"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "overall"[Publication Type] OR "periodical index"[Publication Type] OR "published erratum"[Publication Type] OR "retracted publication"[Publication Type])
Limits: Publication Date from 1996 to 2001, English, Human

Key Questions 3a&b

Name: Hepatitis C (Ques. 3a-3b)
Date and Time search last updated: 26-Sep-2001 11:37:20
Database: PubMed
Search: hepatitis c, chronic[mh] AND hepatocellular carcinoma[mh] AND (diagnosis[mh] OR diagnosis[sh] OR "biological markers" OR ultrasound OR "image interpretation, computer-assisted" OR "alpha-fetoproteins" OR "serologic tests") NOT ("addresses"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "classical article"[Publication Type] OR "clinical conference"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "duplicate publication"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "historical article"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "letter"[Publication Type] OR "meeting report"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "overall"[Publication Type] OR "periodical index"[Publication Type])
Limits: Publication Date from 1996 to 2001, English, Human

Appendix D. Literature Abstract Review Form

Record Number: EPC Hepatitis C - Abstract Review **Reviewer:** _____

First Abstract Review: **Abstract review Form:** **Entered by:_____**

Title:

Do not review, because article (check 1 or more)

1 = not in English
2 = does not include human data
3 = no original data
4 = no information relevant to management of Hepatitis C
5 = reports only basic science
6 = does not apply to one of our key questions
7 = meeting abstract (no full article for review)
8 = other : (specify)_____
9 = unclear : get article to decide

Do not continue if any item above is checked. Otherwise, continue to next column and check *at least one box*.

Article relates to Key Questions (Check all that apply)

☐1a) Does use of **liver biopsy improve outcomes** in management of chronic Hepatitis C? ☐**RCT?**
☐1b) Are results of **initial liver biopsy** related to measures of disease progression and outcomes of treatment? ☐**RCT?**
☐1c) Are results of **followup liver biopsies** related to measures of disease progression and outcomes of treatment? ☐**RCT?**
☐1d) What is the utility of **liver biopsy to identify concomitant** liver disease in patients with Hepatitis C? ☐**RCT?**
☐1e) How well do **non-invasive measures of fibrosis** predict findings of liver biopsy in chronic Hepatitis C? ☐**RCT?**
☐2a) What is **efficacy of current treatment options** for chronic Hepatitis C (pegylated interferon, interferon plus ribavarin, or interferon monotherapy)? ☐**RCT?**
☐2b) See Q2a.
☐2c) What are **outcomes of treatment of chronic Hepatitis C** in subgroups? ☐**RCT?**
☐3a) What is the **efficacy of screening tests for HCC** to improve outcomes in chronic Hepatitis C? ☐**RCT?**
☐3b) What are the sensitivity, specificity and predictive **value of screening tests** in detecting resectable HCC in chronic Hepatitis C? ☐**RCT?**

☐ **Reference only**		☐ **Pediatric patients**
☐ **Systematic review**	☐ **Meta-analysis**	☐ **Case report**

Appendix E. Study Quality Review Form - Johns Hopkins Evidence-based Practice Center Hepatitis C Project

Article ID# _____

First author _____ 1st reviewer (initials) _____ 2nd reviewer (initials) _____

Primary reasons for exclusion: (Check all that apply)

- ☐ Not in English
- ☐ Does not include human data
- ☐ Does not apply to one of our key questions
- ☐ Other: (specify): _____
- ☐ Reports only basic science
- ☐ No information relevant to management of Hepatitis C
- ☐ Meeting abstract (no full article for review)
- ☐ All data reported in a subsequent publication

Additional exclusions per Key Question refinements: (Check all that apply)

- ☐ Addresses only KQ1d (Utility of liver biopsy for identifying concomitant liver disease)
- ☐ Addresses KQ2a or c, except not a randomized controlled trial
- ☐ Addresses only KQ2a, but only interferon alone without analysis of subgroups of interest (e.g., patients with renal disease or inability to take ribavirin)
- ☐ Addresses only KQ2b (Extent of inclusion of patient subgroups in randomized controlled trials)
- ☐ Addresses KQ2d, but has < 5 years (60 months) of followup

Study quality exclusions: (Check all that apply)

For all Questions

☐ **Outcomes were not measured using an appropriate objective standards.**

Objective Standards:

For Q1b, c: Virologic and/or histologic measures

For Q1e: Liver biopsy with at least 1 cm length or 3 portal triads

For Q2a, c, d: Virologic and/or histologic measures

For Q3a: Histologic/pathologic evidence (in at least 50% of patients with abnormal screening tests, and at least 6 months of followup) and/or mortality

For Q3b: Histologic/pathologic evidence

☐ **Total study population < 30** (specify N:_____)

For key questions 1b, 1c, 2a, 2c, and 3a

☐ **The planned length of followup was less than 6 months**

If ANY of the above items is CHECKED ➜STOP: Do Not Continue; return article and form to Mollie

Does article address a Key Question? (Check all that apply)

Biopsy

☐ KQ1a: Deleted

☐ KQ1b: How well do results of **initial liver biopsy** predict measures of disease progression and treatment outcome?

☐ KQ1c: How are results of **followup liver biopsies** related to measures of disease progression and treatment outcome?

☐ KQ1d: Deleted

☐ KQ1e: How well do **non-invasive measures** of fibrosis predict the findings of liver biopsy?

Treatment options

☐ KQ2a: To what extent have **randomized controlled trials** shown the **efficacy and safety of current treatment options** for chronic Hepatitis C (pegylated interferon, interferon plus ribavarin, or interferon)?

☐ KQ2b: Deleted

☐ KQ2c: According to randomized controlled trials, what is the **efficacy and safety of current treatment options** for chronic Hepatitis C in subgroups (e.g., by age, viral genotype, prior treatment status, or presence of cirrhosis, decompensated liver disease, Hepatitis B, or HIV)?

☐ KQ2d: What are the **long term outcomes** (≥5 years) of current treatment options for chronic Hepatitis C

Screening tests

☐ KQ3a: What is the **efficacy of screening tests for hepatocellular carcinoma** to improve outcomes in chronic Hepatitis C?

☐ KQ3b: What are **sensitivity, specificity and predictive value of screening tests** for detecting curable hepatocellular carcinoma in Hepatitis C patients?

REPRESENTATIVENESS OF STUDY POPULATION

6. Did the study describe the setting and population from which the study sample was drawn, and the dates of the study?

a. Adequate	(Setting AND population described AND start and end date specified)	2
b. Fair	(One or more of these NOT reported OR poor description)	1
c. Inadequate	(Not specified)	0
d. Not applicable		N/A

7. Were detailed inclusion/exclusion criteria provided?

a. Adequate	(Detailed description of specific inclusion and exclusion criteria OR statement that all eligible patients enrolled)	2
b. Fair	(Some description, but would be difficult to replicate based on information provided)	1

c. Inadequate	(Minimal description or none at all)	0
d. Not applicable		N/A

8. Was information provided on excluded or not participating patients?

a. Adequate	(All reasons for exclusion AND # excluded OR no exclusions)	2
b. Fair	(Only one of above criteria specified or information not sufficient to allow replication)	1
c. Inadequate	(None of the above criteria specified)	0
d. Not applicable		N/A

Item 9 for key question 1 only

9. Did the study include an appropriate spectrum of patients with chronic hepatitis C? (e.g., not only elderly patients with, for example, decompensated liver disease)?

a. Adequate	(Wide range of age AND wide range in severity of disease)	2
b. Fair	(Wide range of age OR wide range in severity of disease)	1
c. Inadequate	(Neither)	0

10. Does the study describe key patient characteristics at enrollment?

***Demographics*:** age; gender

Hepatitis C Features: genotype; degree of fibrosis or cirrhosis; minimal or decompensated liver disease

a. Adequate	(Demographic and Hepatitis C features well described)	2
b. Fair	(Only demographics well described)	1
c. Inadequate	(No key patient characteristics well described)	0
d. Not applicable		N/A

BIAS AND CONFOUNDING

POINTS

Item 11 for key questions 2a, 2c, 2d, and 3a

11. Was assignment of patients to study groups randomized?

a. Yes	(Investigators could not predict assignment)	2
b. Partial	(Date of birth, admission date, hospital record number, or other non-random scheme for assignment OR did not state method of randomization)	1
c. Not randomized		0
d. Unclear		0
e. Not applicable		N/A

Item 12 for key questions 2a, 2c, 2d, and 3a

12. Did the patient groups have any important differences on key patient characteristics?

***Demographics*:** age; gender

Hepatitis C Features: e.g., genotype, degree of fibrosis or cirrhosis, minimal or decompensated liver disease

a.	Groups equivalent in all factors examined	2
b.	Groups have minor difference in 1 or 2 factors	1.5
c.	Groups have an important difference in one or more factors OR minor differences in more than 2 factors	1
d.	Analysis not done	0
e.	Not applicable	N/A

Item 13 for key questions 2a, 2b, 2d, and 3a

13. Was there blinding of clinicians, patients, and outcome assessors?

a. Excellent	(All three blinded, including all treatment arms)	2
b. Good	(Only 2 of the 3 blinded, or some but not all of the arms blinded in all 3 ways)	1.5
c. Fair	(Only 1 of the 3 blinded)	1
d. Poor	(No blinding or not stated)	0
e. Not applicable		N/A

Item 14 for key questions 1b, 1c, 1e, 3b

14. Was there an independent blind comparison with a reference standard (i.e., virologic/histologic evidence for 1b or c, histologic evidence for 1e, and histologic/pathologic evidence for 3b) at initial assessment and a blinded assessment or follow up?

a. Adequate	(Independent AND blind)	2
b. Fair	(Independent OR blind)	1
c. Inadequate	(Neither)	0
d. Not applicable		N/A

DESCRIPTION OF THERAPY/MANAGEMENT

Item 15 for key question 1 only

15. Did the study describe the technique and size of the liver biopsy?

Technique: Percutaneous transhepatic or transjugular
Sample size: Length and/or number of portal triads

a. Adequate	(BOTH characteristics described)	2
b. Fair	(ONE characteristic described)	1
c. Inadequate	(NEITHER described)	0
d. Not applicable		N/A

Item 16 for key question 2 only

16. Did the study describe details of the treatment regimen?

a. Adequate	(Name of drugs, dose, AND duration described)	2
b. Inadequate	(One of more of above NOT described)	0
c. Not applicable		N/A

Item 17 for key question 3 only

17. Did the study describe details of the screening test(s)?

a. Adequate	(Exact type of test AND frequency of test described)	2
b. Fair	(Exact type of test OR frequency of test described)	1
c. Inadequate	(Neither described)	0
d. Not applicable		N/A

Item 18 for key questions 2a, 2c, 2d, and 3a

18. Was there a description of other treatments and tests given to each study group?

Other treatments: Anti-retroviral drugs, antidepressants, erythropoietin, granulocyte colony stimulating factor, etc.
Other tests: Serologic, virologic, radiologic, etc.

a. Adequate	(Other treatments and tests fully described)	2
b. Fair	(Some description, but information not sufficient to allow replication)	1
c. Inadequate	(Not described or not mentioned)	0
d. Not applicable		N/A

OUTCOMES AND FOLLOWUP

19. Did the study describe complications, side effects, and adverse reactions experienced by patients?

Biopsy: Pain, bleeding, infection, death
***Treatment*:** Depression, thyroid dysfunction, cytopenia, portal hypertension
***Screening*:** Contrast reactions, procedure complications

a. Adequate	(Complications, side effects, AND adverse reactions described fully)	2
b. Fair	(Complications, side effects, OR adverse reactions mentioned, but NOT described fully)	1
c. Inadequate	(Complications, side effects, AND adverse reactions NOT mentioned)	0
d. Not applicable		N/A

20. Was there a description of the criteria for determining outcomes?

a. Adequate	(Clear definitions of each outcome AND exact techniques to assess the outcome)	2
b. Fair	(Some description, but information not sufficient to allow replication)	1
c. Inadequate	(No information provided)	0
d. Not applicable		N/A

21. No item 21

22. Did the study report the numbers of and reasons for withdrawals from the study protocol or patients otherwise lost to follow-up?

a. Numbers and reasons reported (or no withdrawals)	2
b. Only numbers OR reasons reported	1
c. Neither given	0
d. Not applicable	N/A

23. What was the greatest percentage of patients in a treatment/screening study group that withdrew from the study protocol or were lost to follow-up?

a. None	2
b. < 10%	1.5
c. 10 - 20%	1
d. >20%	0
e. Not stated	0
f. Not applicable	N/A

Item 24 for key questions 1b, 1c, 2a, 2c, 2d, and 3a

24. What was the planned length of followup?

a. > 5 years	2
b. 1-5 years	1.5
c. 6 - 11 months	1
d. 0 - 5 months	0
e. Not applicable ***(key question 1e and 3b)***	N/A

STATISTICAL QUALITY AND INTERPRETATION

25. For primary endpoints, did the study report the magnitude of difference between groups (or magnitude of association between key variables) AND an index of variability (e.g., test statistic, *p* value, standard error, confidence interval)?

a. Adequate	(Both reported, with standard error or confidence intervals as index of variability)	2
b. Fair	(Both reported, with only test statistic or *p* value as index of variability)	1
c. Inadequate	(No information given)	0
d. Not applicable		N/A

26. Was the statistical test for all analyses clearly identified?

a. Adequate	(Identified for all analyses)	2
b. Fair	(Identified for some of the analyses)	1
c. Inadequate	(Not identified)	0
d. Not applicable		N/A

Item 27 for key questions 2a, 2c, 2d, and 3a

27. If groups were not comparable at study onset, was there adjustment for potential confounders with multivariate or stratified analyses AND were confounders coded in a way to make such control adequate?

a. Adequate	(Adjustment AND confounders appropriately coded)	2
b. Fair	(Adjustment BUT confounders not coded appropriately OR coding unclear)	1
c. Inadequate	(No adjustment OR not mentioned)	0
d. Not applicable		N/A

28. Were withdrawals, crossovers, and loss to follow-up handled appropriately in analysis?

a. No loss to followup, withdrawals, or crossovers	2
b. Sensitivity analysis	2
c. By intention to treat/screen	2
d. By 'intervention received' analysis only	1
e. By none of the above	0
f. Unknown	0
g. Not applicable	N/A

CONFLICT OF INTEREST

29. Did the study report identify the source of funding and the type and degree of involvement of the funding agency?

a. Adequate	(Source AND type or degree of involvement OR no funding)	2
b. Fair	(Source only)	1
c. Inadequate	(Neither)	0
d. Not applicable		N/A

THANK YOU for your time and attention to completing this work.
Please return completed form to Mollie.