Contents

The Course and Outcome of Hepatitis C

Jay H. Hoofnagle, M.D.

Hepatitis C is caused by a small RNA virus that belongs to the family flaviviridae and is the sole member of the genus hepacivirus. First identified in 1989, the hepatitis C virus (HCV) has a single-stranded RNA genome that is ~ 9.6 kilobases in length and encodes a single, large polyprotein of ~ 3000 amino acids. The HCV polyprotein is cleaved post-translationally into multiple structural and non-structural peptides: structural components consist of a nucleocapsid core [C] and two envelope glycoproteins [E1 & E2] and the non-structural proteins are labeled NS2 through NS5. The specific functions of the individual NS proteins have not been completely elucidated. NS3 has both helicase and protease activities and the NS5 region contains the RNA-dependent RNA polymerase activity essential for RNA viral replication. These enzymatic activities are potential targets for antiviral compounds. HCV RNA also has important and highly conserved 5' and 3' untranslated regions (UTRs). The 5' UTR has an internal ribosomal entry site (IRES) essential for initiation of viral protein translation and the 3' UTR has structured RNA elements essential for both viral replication and translation.

There are neither robust cell culture systems for propagation of HCV nor simple small animal models of the infection, so the replicative cycle of the virus has largely been deduced from that of other flaviviruses. HCV replicates in the cytoplasm of hepatocytes where it is not directly cytopathic. Persistent infection appears to rely upon rapid production of virus and continuous cell-to-cell spread along with a lack of vigorous T cell immune response to HCV antigens. The HCV RNA genome mutates frequently and circulates in serum not as a single species but as a population of quasispecies with individual viral genomes differing by 1 to 5 percent in nucleotide sequence. Six major genotypes (1 to 6) and more than 50 subtypes (e.g., 1a, 1b, 2a, 2b) have been described. Different isolates of HCV differ by 5–15 percent, subtypes by 10–30 percent, and genotypes by as much as 30–50 percent in nucleotide sequence.

Hepatitis C can cause both acute and chronic hepatitis. Knowledge of the course and outcome of infection arises largely from studies in chimpanzees and previous post-transfusion and more current post-needlestick accident cases of hepatitis C. In acute hepatitis, HCV RNA can be detected in the serum within one to two weeks after exposure, rising thereafter to levels of 10^5 to 10^7 viral genomes per ml. Serum alanine aminotransferase (ALT) levels indicative of hepatocyte injury and necrosis start to rise 2 to 8 weeks after exposure and usually reach levels of greater than 10 times the upper limit of normal. About one-third of adults with acute HCV infection develop clinical symptoms and jaundice, the symptomatic onset ranging from 3 to 12 weeks after exposure. In self-limited acute hepatitis C, symptoms last for several weeks and subside as ALT and HCV levels fall. Acute hepatitis C can be severe and prolonged but is rarely fulminant. Antibody to HCV as detected by enzyme immunoassay (EIA) arises at the time of or shortly after onset of symptoms, so that 30 percent of patients test negative for anti-HCV at onset of symptoms, making anti-HCV testing unreliable in diagnosis. Almost all patients eventually develop anti-HCV, although titers can be low or even undetectable in patients with immune deficiencies.

Chronic hepatitis C is marked by persistence of HCV RNA for at least six months after onset of infection. The chronicity rate of hepatitis C averages 70–80 percent, but varies by age, sex, race, and immune status. During the evolution of acute to chronic infection, HCV RNA and ALT levels can fluctuate markedly, some patients having periods during which HCV RNA is undetectable and ALT levels normal. Once chronic infection is established, however, serum HCV RNA levels tend to be stable. Most patients with chronic hepatitis C have few if any symptoms, the most common being fatigue, which is typically intermittent. Right upper quadrant pain (liver ache), nausea, and poor appetite occur in some patients. Serum ALT levels are usually continuously or intermittently elevated, but the height of elevations correlates poorly with disease activity and at least one-third of infected persons have persistently normal ALT levels. In these patients, the underlying disease is usually, but not always, mild and non-progressive. Liver histology in chronic HCV infection demonstrates chronic mononuclear cell infiltration in the parenchyma and portal areas, focal hepatocyte necrosis, and variable degrees of fibrosis.

The major long-term complications of chronic hepatitis C are cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC), which develop only in a proportion of patients and only after many years or decades of infection. Progression to cirrhosis is often silent clinically and some patients are not known to have hepatitis C until they present with the complications of end-stage liver disease or HCC. Once cirrhosis is present, the ultimate prognosis is poor.

Other complications of chronic hepatitis C can be important and affect quality of life. The major extrahepatic manifestations of chronic HCV infection are cryoglobulinemia, glomerulonephritis, seronegative arthritis, sicca syndrome, and porphyria cutanea tarda. HCV-related cryoglobulinemia is the most common: up to 40 percent of patients with chronic hepatitis C may have low levels of cryoglobulins in serum, but only 1 percent have symptomatic cryoglobulinemia with fatigue, arthralgias, skin rash, renal disease, or neuropathy.

Thus, the course of hepatitis C is variable, the severity of illness ranging from a transient, self-limited and asymptomatic infection to a chronic, progressive liver disease that leads ultimately to cirrhosis and HCC.

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The Burden of Hepatitis C in the United States

W. Ray Kim, M.D., M.Sc., M.B.A.

Incidence and Prevalence

Disease frequency may be measured either by the pool of existing cases (prevalence), or by the occurrence of new cases (incidence). The most widely quoted data on the prevalence of HCV in the United States are derived from the third National Health and Nutrition Examination Survey (NHANES), a national survey of a representative sample of non-institutionalized civilian Americans conducted between 1988 and 1994. Of 21,000 people tested for HCV, 380 people (1.8 percent) carried antibodies against the virus (anti-HCV), of whom 280 (74 percent) had detectable viral RNA in their serum. These numbers project to 3.9 million Americans (95 percent confidence interval (CI): 3.1–4.8 million) who have been infected with HCV, of whom 2.7 million (95 percent CI: 2.4–3.0 million) have ongoing chronic infection. Hepatitis C is **the most common chronic blood-borne infection in the United States**.

While HCV is a reportable infectious disease in the United States, the incidence of new HCV infection is much more difficult to estimate than its prevalence. Since the majority of acute HCV infections are not accompanied by recognizable symptoms and thus not reported, enumerating reported cases of acute hepatitis C significantly underestimates the true incidence of hepatitis C infection. Nonetheless, the Centers for Disease Control and Prevention (CDC) estimate that the annual incidence of acute HCV infection in the United States decreased from an average of approximately 230,000 new cases per year in the 1980s to 38,000 cases per year in the 1990s.

It may be expected that the reduction in new incident cases will eventually lead to a decrease in the prevalence of HCV. A report from CDC projected that, following a peak in the mid-1990s at slightly above 2.0 percent, the HCV prevalence would gradually decrease to 1.0 percent by 2030. While the prevalence of **HCV infection** may be decreasing, **the prevalence of liver disease caused by HCV is on the rise**. This is because there is a significant lag, often 20 years or longer, between the onset of infection and clinical manifestation of liver disease. CDC projects a fourfold increase in the number of persons with longstanding (20 years or longer) infection between 1990 and 2015. Furthermore, it is uncertain whether the projected decline in the HCV prevalence based on NHANES data (non-institutionalized civilians) translates to other population groups known to have very high prevalence of HCV. Examples of these groups include patients at Veterans Affairs (VA) hospitals, active intravenous drug users, and prison inmates.

Mortality from HCV

Chronic liver disease is one of the 10 most common causes of death in the United States. Figure 1 summarizes the secular trend in liver-related mortality in the United States. There has been a steady increase in the number of deaths from liver disease over time. The increase was mainly **attributable to viral hepatitis and hepatic malignancies**. On the other hand, the age-adjusted death rate (deaths per 100,000 living persons, adjusted to 2000 population census) from liver disease has been relatively constant.

Mortality statistics in the United States are based on the "underlying cause of death" listed on death certificates. As deaths attributable to viral hepatitis primarily result from chronic liver disease and liver failure and, in those cases, viral hepatitis may not necessarily be listed as the underlying cause of death, it is likely that deaths classified as viral hepatitis underestimate the true incidence of deaths related to viral hepatitis. Further, until 1999, when the International Classification of Disease version 10 (ICD-10) began to be used to classify causes of death, HCV was not given an independent code, making it difficult to estimate the total number of deaths attributable to HCV.

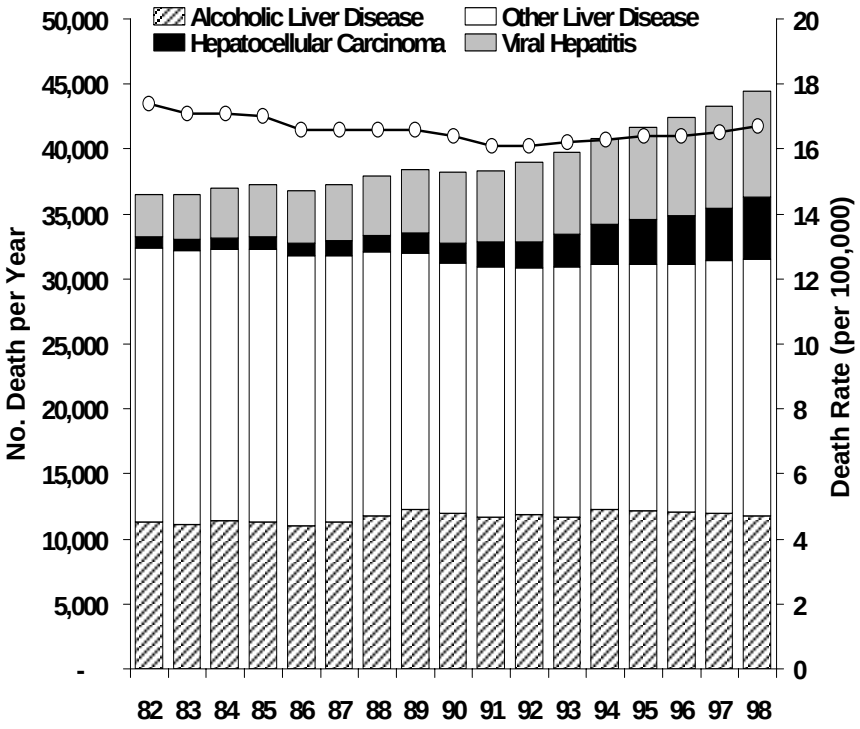

Figure 1. Mortality from Liver Disease in the United States (82–98).[4]

Bars represent number of deaths (axis on the left) from viral hepatitis, whereas dots represent death rate (axis on the right). The top two bars (viral hepatitis and hepatocellular carcinoma) mainly account for the rise in deaths.

With these caveats in mind, there was a sixfold increase in the number of deaths from viral hepatitis (all types) between 1982 (n=814) and 1999 (n=4853). In 1999, the first year HCV was reported separately, **the majority (77 percent, n=3759) of deaths from viral hepatitis were due to HCV**. During the same period, there was a commensurate increase in the age-adjusted death rate from 0.4 to 1.8 deaths per 100,000 persons per year. To estimate the degree of under-reporting of HCV as the underlying cause of death in the mortality data, the number of in-hospital deaths from liver disease related to hepatitis C was enumerated (see below for details). In 1998, there were an estimated 4500 in-hospital deaths in the United States for liver disease related to HCV (source: Healthcare Utilization Project, AHRQ).

Morbidity and Health Care Cost from HCV

As chronic hepatitis C has a prolonged natural history and it is only a relative minority of the infected that require ongoing medical care for their hepatitis, it is difficult to estimate the magnitude of morbidity at the population level. A cost-of-illness study conducted by the American Gastroenterological Association estimated that there were 317,000 outpatient visits for the treatment of hepatitis C in the United States in 1998. The cost for outpatient physician services was projected to be $23.9 million. During the same year, $530 million was spent for antiviral treatment of HCV.

Patients with more advanced stage liver disease present with portal hypertension and hepatic decompensation, as manifested by ascites, hepatic encephalopathy, or gastrointestinal bleeding, which often necessitates inpatient care, including liver transplantation. End-stage liver disease and/or hepatocellular carcinoma related to HCV is already the **most common indication for liver transplantation in the United States**. In 1999, approximately one-third of available cadaveric livers were transplanted into recipients with HCV infection.

The nationwide impact of liver disease due to HCV has been estimated based on data derived from the Nationwide Inpatient Sample of the Healthcare Utilization Project. This database represents a 20 percent stratified sample from all non-Federal, acute-care hospitals, which account for approximately 95 percent of all hospitalizations in the nation. As liver disease from HCV may not be the main reason for all hospitalizations with a HCV diagnosis, hospitalizations were divided into three groups. These included hospitalizations in which liver disease from hepatitis C was the primary reason for hospitalization, those in which liver disease from HCV was a secondary reason, and those in which HCV was an incidental notation. Because of the uncertainty of ascertainment of HCV in the early 90s, hospitalizations for other chronic hepatitis (non-A, non-B) were also captured.

There was an almost **fourfold increase during the five-year period between 1993 (n=35,700) and 1998 (n=134,200)** in the total number of hospitalizations in which HCV was mentioned in the discharge diagnosis. Some of the increase was due to lack of ascertainment of HCV in the early 1990s, as there was a partially corresponding decrease in the non-A, non-B hepatitis hospitalizations (from 69,600 in 1993 to 47,800 in 1998). The number of hospitalizations in which liver disease was the principal diagnosis increased from 10,100 to 32,800 and secondary diagnosis from 6,000 to 27,100 between 1993 and 1998. As expected, the increase in hospital services for HCV-related morbidity was accompanied by a similar increase in hospital charges. Hospitalizations were given differential weight depending on the relevance of hepatitis C (principal diagnosis vs. incidental notation). After adjustment for inflation (1998 US$), **the total hospital charges for 1998 were slightly over 1 billion dollars** nationwide. This represents doubling in three years ($528M for 1995) and tripling in five years ($348M for 1993).

Summary

Hepatitis C infection is common, affecting nearly 2 percent of the general population and a much higher percentage of people under special circumstances. Since the early 1990s, national statistics indicate that morbidity, mortality, and health care utilization associated with consequences of long-standing infection with hepatitis C are increasing in epidemic proportions. Future projection studies predict that the increase will continue in the foreseeable future.

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Natural History of Chronic Hepatitis C

Leonard B. Seeff, M.D.

Introduction

The rationale for establishing the natural history of any disease is to inform both the patient and physician of future expectations and to assess the need for treatment. Unfortunately, the characteristics of hepatitis C—its silent onset, evolution to a generally asymptomatic and greatly prolonged chronic phase, its co-mingling with other morbid conditions, and the fact that treatment that alters the course is now almost routine—have limited the ability to accurately define its natural history. Several strategies have been used for this purpose, all of which have their drawbacks but still have provided useful information. Because of the many inherent difficulties, there is much controversy regarding the natural history of hepatitis C. The outcome of concern is increasing fibrosis progression, culminating in cirrhosis and, occasionally, advancement to hepatocellular carcinoma (HCC). Some believe this sequence to be common; others believe that serious progression is relatively limited. Both of these views may be valid, both identifying a frequency of progression that is modified by differing demographic characteristics of the population studied and by varying intrinsic and extrinsic factors. In essence, the controversy derives from the uncertainty of whether or not fibrosis progression is linear.

Advancement from Acute to Chronic Hepatitis

The natural history is a product of the outcome of the acute infection as well as the outcome of the subsequent chronic hepatitis. A problematic issue is the actual timing of evolution to chronic hepatitis. Traditionally, this has been based on persistence of virus for at least 6 months. However, viremia may persist beyond this time, although it is believed that loss of virus after one year is exceptional. Prospective study has indicated that chronic hepatitis evolves in about 85 percent of acutely infected persons. On the other hand, cross-sectional studies of large, untreated anti-HCV positive cohorts, consisting mainly of young persons, many of them female, have reported absent virus in as many as 45–50 percent of instances, implying a higher rate of spontaneous recovery in some groups. Thus, spontaneous recovery from acute hepatitis C occurs in 15–45 percent of instances.

Progression to Cirrhosis

Once chronic hepatitis has developed, the question then is: What are the long-term sequelae? Numerous efforts have been made to define the frequency and rate of progression to cirrhosis and HCC. Evident in all these studies is that clinically overt liver disease is generally not seen in the first two decades following the acute infection. This does not imply that cirrhosis does not evolve during this period, but the actual timing of its onset cannot be determined without performing serial liver biopsies. Early reports, based largely on retrospective studies, indicated that, at the end of two decades of infection, about 20 percent had developed cirrhosis,

although some of the studies have reported rates of almost 50 percent. The drawbacks of retrospective studies are that evaluation is limited to those who have achieved an end point and that tracing to disease onset is hindered by the paucity of symptoms at onset. Thus, ascertainment bias may exist using this approach. Later prospective studies, mainly of HCV-infected transfusion recipients, reported a lower rate of development of cirrhosis (7–16 percent), but most of these studies were too short in duration to provide an accurate assessment of the ultimate outcome. Even lower rates of cirrhosis have been reported among several groups in whom it was possible to trace back far in the past to the time of onset or near onset. Thus, among children infected through transfusion in the first years of life and traced 20 years later, and among young women infected through receipt of HCV-contaminated Rh immunoglobulin and traced over approximately the same time period, cirrhosis was noted to have occurred in about 2 percent. A similar rate was noted in a 45-year followup of young HCV-positive military recruits who had been bled at the time of serving on a military base, the samples having been retained in a repository. The common theme of this lower rate of cirrhosis is that it was noted among persons infected at a young age.

Taking the numerous variety of studies into account, a group of Australian investigators who reviewed the world's literature for the rate of cirrhosis development at 20 years concluded that the studies could be divided into 4 broad categories: those performed in liver clinics, the mean cirrhosis rate being 22 percent (95 percent CI, 18–26 percent); post-transfusion hepatitis studies, with a mean of 24 percent (11–37 percent); studies of blood donors, with a mean of 4 percent (1–7 percent); and studies of community-based cohorts, with a mean of 7 percent (4–10 percent). They concluded that selection bias accounted for the two higher rates, and that the community-based cohort studies appeared more representative in estimating disease progression at a population level. These data provide useful figures for the frequency of progression to cirrhosis two decades after acute infection that appears to range between about 2–4 percent to 20–25 percent, depending on several factors, to be described below. However, many of those infected are young and are destined to live for several more decades. Therefore the question that must be posed is: What happens after the first two decades with regard to liver disease progression? Does fibrosis progression continue to increase at a linear rate? Does the rate level off and remain the same throughout life? Does fibrosis progression increase as age advances? Certainly, many chronically infected persons are known to live for a lifetime without succumbing to liver disease, whereas others are known to develop end-stage liver disease 30 to 60 years after acute infection. Thus, these questions can only be answered by conducting markedly extended studies, few of which have been accomplished for obvious reasons. Other approaches have been to model the expected outcome based on preconceived notions, models that may or may not turn out to be valid. Most important, is it possible to predict in the individual HCV-infected person what the outcome is likely to be? The answer is a qualified *maybe*, taking into account the many factors that might enhance progression.

Factors That May Determine Progression

The differing outcomes suggest that there are variables that may contribute to the rate of liver disease progression. These can be considered as being viral-related, host-related, or a consequence of external factors.

Viral-Related

Factors that might contribute include viral load, viral genotype, and quasispecies diversity. There is little evidence to indicate that viral load plays a role in disease progression; there are suggestions that progression is more likely following infection with genotypes 1a and 1b than genotype 2, although this has been disputed, most studies now reporting that there is no effect of genotype characteristics on disease outcome. While the degree of quasispecies diversity appears to play a role in evolution from acute to chronic hepatitis, there is no evidence that it enhances progression of already established chronic hepatitis.

Host-Related

One of the most important determinants is age at the time of infection, the relationship being an inverse one. What is not yet established is whether the relatively mild disease seen two decades after infection of young people will begin to accelerate with increasing age. This brings into account the fact of duration of infection, since it is rare although not unheard of, to identify end-stage liver disease in under one-and-a-half to two decades. Perhaps the flourishing of liver disease with time may be a consequence in part of age-related immune depression. Certainly, an immune suppressed state vigorously enhances disease progression as is noted among infected persons with hypogammaglobulinemia and, especially, HIV co-infection. Hepatitis B and schistosomal co-infection also increase disease progression perhaps through induced immune dysfunction as well as through direct cytotoxicity. Genetic background also may be of importance. Genes of the major histocompatability complex appear also to play a role, not so much in fibrogenesis, but in clearance of the virus. HLA class I antigens seem to be associated with viral persistence whereas class II antigens (DRB1 alleles) are identified more frequently in those who clear virus and therefore have milder disease. Inheritance of high TGF-β1 and angiotensinogen-producing genotypes has been linked to fibrosis progression. Co-morbid conditions such as hemochromatosis and non-alcoholic steatohepatitis are also associated with advancing chronic liver disease. In addition, outcome may be influenced by gender and race. Females are reported to have a slower rate of progression, a finding that seems to be emerging also among African-Americans. Finally, the expression of the disease plays a role in outcome. HCV-infected persons with raised aminotransferase levels are far more likely to develop progressive liver disease than are those with normal serum enzymes.

External Factors

Clearly, associated chronic alcoholism is a powerful co-factor in liver disease progression. Yet to be determined is what is the least amount of alcohol and the type of drinking pattern that plays a role in advancing chronic hepatitis C. Also of note are the data suggesting that smoking may increase disease progression. Exposure to toxic products, either in the form of administered drugs that may be hepatotoxic or as environmental contaminants, may have important effects. It is noteworthy that death associated with chronic hepatitis C in the United States is more likely to be a result of end-stage liver disease rather than HCC, whereas in Japan, virtually all deaths are attributed to HCC. It has been suggested that the difference is a consequence of a longer duration of HCV infection in Japan than in the United States, a view

that may or may not be valid. Another possible explanation is that toxic environmental contaminants may play a contributory role in Japan.

Progression From Cirrhosis to HCC

HCC rarely (if ever) develops in persons with chronic hepatitis C without preceding cirrhosis or significant fibrosis. The strongest evidence for a relationship between HCV infection and HCC comes from Japan, but supporting evidence comes from many other countries including the United States, Italy, Spain, Egypt, France, and elsewhere. Recent evidence indicates that the incidence of HCC increasing in the United States is presumed to be a consequence of the mushrooming of hepatitis C infection in the 1960s and 1970s. The data in the United States indicate that once cirrhosis has developed, HCC evolves at the rate of 1–4 percent per year. The figure in Japan is even higher.

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Fibrosis and Disease Progression

Patrick Marcellin, M.D.

Chronic infection with HCV is associated with the typical histological features of chronic hepatitis including hepatocellular necrosis and inflammation (activity or grade) and fibrosis (stage). While the activity of the chronic liver disease can fluctuate over time, the stage of fibrosis is believed to be progressive and largely irreversible. In chronic hepatitis C, the rate at which fibrosis progresses varies markedly. In some individuals, fibrosis ultimately leads to cirrhosis, which is associated with the major complications of the liver disease: portal hypertension, liver failure, and hepatocellular carcinoma. In others, fibrosis does not appear to progress even after decades of infection. For these reasons, assessment of the stage and rapidity of progression of fibrosis can be helpful in determining the prognosis and the need for therapy in the individual patient. Factors associated with fibrosis progression are not well defined and the role of necroinflammatory activity is still controversial.

Assessment of the Stage of Fibrosis

Liver biopsy remains the gold standard to assess fibrosis. Several systems for scoring liver fibrosis have been proposed, each based upon visual assessment of portal and periportal fibrosis. The more frequently used systems are the Histology Activity Index (HAI: Knodell score), the Ishak modification of the HAI score, and the METAVIR. The HAI scoring system ranges from 0 to 22 and fibrosis is staged as 0, 1, 3, and 4. This discontinous scale was developed to allow for clear separation of mild (1+) from extensive (3+) fibrosis which has important prognostic value. The HAI system is simple and has been widely used, particularly in the large multicenter trials of interferon and ribavirin therapy of chronic hepatitis C. However, the intra- and inter-observer reproducibility of the HAI is not very good and distinction between stages 1 and 3 may be difficult. In addition, its discontinous scale complicates statistical analysis in clinical trials.

The modification of the HAI scoring system proposed by Ishak et al. is more sensitive in assessing fibrosis. Fibrosis stage is scored continuously from 0 to 6, which permits a better assessment of the effect of therapy on fibrosis. The Ishak score is better validated and gives a more accurate assessment of fibrosis.

The METAVIR scoring system is simple; fibrosis stages are scored continuously from 0 to 4. This system has been carefully validated in large groups of patients with chronic hepatitis C and has shown good intra- and inter-observer reproducibility.

Important limitations of these scoring systems should be emphasized. Hepatic fibrosis may not be homogenous throughout the liver and the liver specimen obtained by needle biopsy may not accurately reflect the overall average degree of fibrosis. The reliability of the assessment of fibrosis stage increases with the size of the liver sample. In most studies, a minimum length of 10 mm is required. Regardless of biopsy length, however, fibrosis may be underestimated and cirrhosis missed in some patients.

Factors Associated With the Stage of Fibrosis

Most cross-sectional studies of large numbers of liver biopsies have shown that the stage of fibrosis is associated with patient age, the age at onset of infection, male sex, a history of heavy alcohol consumption, and the presence of immune deficiency, such as HIV co-infection or immunosuppressive therapy. The mechanisms by which age and sex affect the degree of fibrosis are not known. Alcohol, which by itself can cause liver disease and fibrosis, may worsen fibrosis in hepatitis C at amounts that are not injurious in non-infected persons, but the amount of alcohol beyond which the progression of fibrosis is increased is unknown.

Serum biochemical tests do not reliably predict the stage of fibrosis. Currently available, indirect serum markers of fibrosis are not reliable, particularly in discriminating between mild and moderate degrees of fibrosis. In cross-sectional studies, serum alanine and aspartate aminotransferase (ALT and AST) levels do not correlate well with fibrosis. However, patients with documented, persistently normal ALT levels usually have mild degrees of hepatitis and either no or mild stages of fibrosis. The association between fibrosis stage and the necroinflammatory activity scores on liver biopsy is controversial. Necroinflammatory activity is a dynamic process in chronic hepatitis C and may fluctuate over time. Therefore, the activity score reflects the severity of necrosis and inflammation at a given point.

Factors Associated With Progression of Fibrosis

From retrospective studies and from some prospective studies done in patients infected by blood transfusion at a relatively older age, it is estimated that 20 percent of patients with chronic hepatitis C develop cirrhosis within 20 years of onset. In contrast, studies of cohorts of women who did not drink alcohol and who were infected by Rh immune globulin at a young age indicated that fewer than 5 percent developed cirrhosis within 20 years. These natural history studies validate the importance of age, sex, and alcohol intake in progression of fibrosis.

Cross-sectional studies using mathematical modelling performed on cohorts of patients with a single liver biopsy suggest that the average rate of progression of fibrosis in chronic hepatitis C is 0.133 METAVIR points per year. Based on this rate, the estimate is that cirrhosis develops in the average patient after 30 years. The average delay to the development of cirrhosis ranges from 13 years in infected men aged 40 or more years who drink more than 50 g of alcohol to 42 years in infected women under 40 years of age who do not drink alcohol. Furthermore, the progression of fibrosis is probably not linear. For instance, the time required to progress from stage 0 to 2 may be far longer than the time required to progress from stage 3 to 4. Moreover, fibrosis progression may accelerate with age (particularly after the age of 50). Finally, fibrosis may remain mild and stable for decades and may even regress spontaneously in some patients.

The progression of fibrosis is difficult to predict in the individual patient particularly based upon assessment at one point in time. There are no good clinical, biochemical, or virological tests that predict progression of fibrosis. High serum ALT levels have been associated with more active liver disease and more rapid progression of fibrosis in some prospective studies, which supports the use of monitoring of ALT levels in assessing prognosis and need for therapy. However, the validity of this approach and the level above which the ALT elevations

are predictive of more rapid progression is not known. Virological factors such as serum HCV RNA level and HCV genotype are not predictive of fibrosis. Genotype 3 is associated with more liver steatosis than other genotypes, and steatosis itself, as well as other metabolic factors (such as lipid disorders, obesity, insulin resistance, and diabetes) may also predispose to more rapid progression of fibrosis.

Repeat liver biopsy is the only reliable means of assessing the progression of fibrosis and is commonly recommended every 3 to 5 years in untreated patients. A second liver biopsy can distinguish patients with rapidly progressive fibrosis, but may also merely indicate that the initial biopsy underestimated the degree of fibrosis. Overall, the risk of progression of fibrosis of more than one point in a 3 to 5 year period is low. In patients with factors associated with a higher risk of progression such as age beyond 50 years, alcohol consumption, or high serum ALT levels, liver biopsy may be recommended more frequently (2 to 3 years); in contrast, in the younger patient with no other risk factors, liver biopsies may be performed less frequently (every 5 to 6 years).

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Non-Invasive Monitoring of Patients With Chronic Hepatitis C

Robert J. Fontana, M.D., and Anna S.F. Lok, M.D.

Patients with chronic hepatitis C (CHC) are at risk of developing cirrhosis, liver failure, and hepatocellular carcinoma (HCC). However, specific symptoms and physical findings of chronic liver disease are frequently absent until patients develop hepatic decompensation. Thus, clinical examination is often unreliable in assessing the severity of liver disease in patients with CHC. Liver histology is the gold standard for establishing the severity of liver injury and fibrosis, but this procedure is associated with risks of complications, discomfort, and expense. In addition, sampling error may occur leading to erroneous staging. Nonetheless, information on the extent of hepatic fibrosis or stage of liver disease is important for prognostication as well as for decisions on treatment. As a result, practicing physicians are in need of simple, safe, inexpensive, and reliable means to non-invasively assess the severity of liver disease in patients with CHC.

The initial evaluation of patients with CHC should include a thorough history and physical examination. A PCR assay for HCV RNA is recommended to confirm the presence of viremia because up to 30 percent of individuals who test positive for HCV antibody (anti-HCV) may have resolved infection or a false positive EIA result. Quantitative HCV RNA levels and HCV genotypes do not correlate with disease severity, but these results are useful in predicting the likelihood of an antiviral treatment response. The initial evaluation should include a comprehensive metabolic panel, prothrombin time, and complete blood counts (CBC) with platelets. Serum aspartate and alanine aminotransferase (AST/ALT) levels reflect liver injury, but the correlation with histologic necroinflammatory activity as well as the severity of hepatic fibrosis is poor[1,2]. Serum albumin and bilirubin levels and prothrombin time reflect hepatic function, but these values usually remain normal even in patients with compensated cirrhosis. Thus, routine blood tests cannot differentiate early (minimal fibrosis) from advanced (compensated cirrhosis) stage of liver disease. Among the routine blood tests, decreased platelet count is the earliest indicator of cirrhosis[3]. Other investigators have found that as patients progress from chronic viral hepatitis to cirrhosis, there is reversal of AST/ALT ratio to >1.[4]

Ultrasound is often recommended as part of the initial evaluation of patients with CHC. Ultrasound and other imaging techniques such as CT and MRI can be used to diagnose cirrhosis based on the presence of an enlarged spleen, small nodular liver, ascites, or varices. In addition, these techniques may detect HCC. However, current imaging is unable to assess the extent of hepatic fibrosis and to diagnose early cirrhosis.

Other novel but less well-established non-invasive means of assessing disease severity in patients with compensated CHC are under development. Serum fibrosis markers that reflect the balance between fibrogenesis and fibrolysis have been proposed as a simple, non-invasive means of assessing hepatic fibrosis.[5,6] To date, none of these markers alone correlates well with hepatic fibrosis. Whether a panel of markers such as hyaluronic acid, YKL-40, and PIIINP will replace liver biopsies remains to be determined.[7,8] Contrast-enhanced ultrasound doppler has also been proposed as a simple, non-invasive means of detecting advanced hepatic fibrosis.[9] However, this method has not yet been validated and will require sophisticated instruments and operators

for optimal performance. Radionuclide liver spleen scans can detect the presence of portal hypertension but are insensitive in the diagnosis of early cirrhosis. Similarly, the use of various metabolic probes to assess functional liver mass has been reported to be reliable in differentiating patients with compensated from decompensated liver disease, but these studies are cumbersome and have not been proven to be useful in distinguishing patients with various stages of hepatic fibrosis.[10]

The optimal frequency and types of tests that should be performed for monitoring CHC patients who are not on antiviral therapy have not been determined. In general, tests for CBC and platelets and a comprehensive metabolic panel should be performed every six months. As discussed above, a progressive decrease in platelet counts or a reversal of the AST/ALT ratio suggests the development of cirrhosis. Repeat testing of anti-HCV, HCV RNA level, or HCV genotype is unnecessary and does not provide any information on the stability or progression of liver disease. For patients with known cirrhosis, alfa-fetoprotein testing and ultrasound should be included although the efficacy of these tests in HCC surveillance is low. Upper endoscopy should be performed in patients with cirrhosis, especially those with clinical evidence of portal hypertension, to determine the need for prophylaxis against variceal bleeding. Patients with decompensated cirrhosis may need more frequent monitoring to determine the optimal timing for transplant evaluation. Monitoring may be less frequent in patients with persistently normal aminotransferases and those with minimal hepatic fibrosis after a long duration of infection (slow progressors). Because of the variable natural course of CHC and the possibility of sampling error, many hepatologists recommend repeat liver biopsies in 4–5 years in patients who decide not to receive antiviral treatment based on the finding of early disease at initial evaluation. The availability of non-invasive tests that correlate with progression of hepatic fibrosis will obviate the need for repeat liver biopsies.

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Use and Interpretation of Virologic Tests

Jean-Michel Pawlotsky, M.D., Ph.D.

Two categories of tests are used in the management of hepatitis C virus (HCV)-infected patients: (i) indirect tests that detect antibodies to HCV (anti-HCV); (ii) direct tests that detect, quantify, or characterize viral particle components, such as HCV RNA or core antigen. Direct and indirect virological tests play a crucial role in the diagnosis of infection, therapeutic choices, and assessment of the virological response to therapy.

Indirect Tests

Anti-HCV detection. Anti-HCV is typically detected using second- or third-generation enzyme immunoassays (EIAs) that detect mixtures of antibodies directed to various HCV epitopes. The specificity of currently available EIAs for anti-HCV is higher than 99 percent. Their sensitivity is more difficult to determine in the absence of a more sensitive gold standard. EIAs for anti-HCV detect antibodies in more than 99 percent of immunocompetent patients with detectable HCV RNA. EIAs are sometimes negative despite the presence of active HCV replication in hemodialysis patients or patients with profound immunodeficiencies. Immunoblot tests have been used in the past as confirmatory assays. Given the good performance of the current anti-HCV EIAs, immunoblot tests no longer have utility in the clinical virology setting. They are still useful in the blood bank setting, where the positive predictive value of a positive EIA result is significantly lower than in the diagnostic setting.

Serological determination of HCV genotype. HCV genotype can be determined by detection of type-specific antibodies using a competitive EIA (so-called "serotyping"). This assay provides interpretable results in approximately 90 percent of immunocompetent patients with chronic hepatitis C. Its sensitivity is lower in hemodialysis or immunodepressed patients. The assay identifies the type (1 to 6) but not the subtype of HCV. Concordance with molecular assays is in the order of 95 percent. Currently, no serotyping assay is FDA-approved.

Available Tests

Direct Tests

Qualitative detection of HCV RNA. Qualitative (i.e., nonquantitative) HCV RNA detection assays are useful because they are significantly more sensitive than most available quantitative assays. The qualitative assays are based on the principle of target amplification using either polymerase chain reaction (PCR) or transcription-mediated amplification (TMA). The lower detection cutoffs of the corresponding commercial assays are 50 HCV RNA international units (IU)/ml and 10 IU/ml, respectively. Their specificity is of the order of 98–99 percent. The PCR assay is FDA-approved.

Viral level quantification. HCV RNA level can be quantified by means of target amplification techniques (PCR or TMA) or signal amplification techniques ("branched DNA"

assay). The lower detection cutoffs of the current assays vary between 30 IU/ml and 615 IU/ml, and the upper limit of linear quantification between 500,000 IU/ml and 7,700,000 IU/ml. Samples with a viral level higher than the upper limit of an assay should be retested after 1/10 or 1/100 dilution. Quantification is independent of the HCV genotype. The international unit, recently defined with reference to the WHO HCV RNA standard, should be used in any HCV RNA quantitative assay in order to compare results given by different assays and to apply global recommendations. Variations of less than 0.5 logs (i.e., of less than threefold) should not be taken into account as they may relate to the intrinsic variability of the assays. No HCV RNA quantification assay is approved currently in the United States, but several are likely to be in the future.

Molecular determination of HCV genotype (genotyping). The gold standard for genotyping is direct sequencing of the NS5B or E1 regions. In clinical practice, HCV genotype can be determined by direct sequence analysis, reverse hybridization onto genotype-specific oligonucleotide probes, or restriction fragment length polymorphism analysis after PCR amplification of the 5' noncoding region. Typing errors are uncommon, but subtyping errors may occur in 10–25 percent of cases. These errors may be related to the region studied (5' noncoding) rather than the technique used. Subtyping errors have few clinical consequences because only the genotype is useful for clinical decisions. No genotyping assay is currently approved in the United States.

Detection and quantification of total HCV core antigen. Total HCV core antigen can be detected and quantified by means of EIA assay. The HCV core antigen titer (in pg/ml) correlates closely with HCV RNA level, and thus can be used as an indirect marker of viral replication. However, the current version of the assay does not detect HCV core antigen when HCV RNA is below approximately 20,000 IU/ml. This assay is not FDA-approved.

Practical Use of Virological Tests

The phrase "HCV RNA detection by means of a sensitive technique" used in this presentation refers to a technique with a lower limit of detection of 50 IU/ml or less. Furthermore, in discussing HCV RNA quantitation, it is assumed that the results are within the limits of its range of linear quantification of the assay.

Diagnosis of HCV Infection

Acute hepatitis C. During acute hepatitis of unknown origin, anti-HCV should be tested by EIA and HCV RNA by a sensitive HCV RNA technique. The presence of HCV RNA without anti-HCV is strongly indicative of acute hepatitis C, a diagnosis that can be confirmed by subsequent seroconversion. In the absence of both markers, acute hepatitis C is unlikely. In the presence of both, it is difficult to differentiate acute hepatitis C from an acute exacerbation of chronic hepatitis C or from acute hepatitis of other cause in a patient with chronic hepatitis C.

Chronic hepatitis C. In a patient with chronic liver disease, the diagnosis of chronic hepatitis C can be made based on detection of both anti-HCV and HCV RNA using a sensitive technique. The lack of anti-HCV in the presence of HCV RNA is uncommon in

immunocompetent patients with chronic hepatitis C. It can occur (although rarely with the current EIAs) in hemodialysis or profoundly immunodeficient patients.

Mother-to-infant transmission. The diagnosis of HCV infection in a baby born to an HCV-infected mother should be based on the detection of HCV RNA with a sensitive technique rather than anti-HCV, because antibodies are passively transferred *in utero* and remain detectable for several months to more than a year after delivery regardless of whether transmission occurs. The optimal timing for HCV RNA testing for diagnosis is not known. Appropriate times are 6 to 12 months after birth.

Diagnosis of infection after an occupational exposure. HCV RNA is detectable in serum within one to two weeks after an accidental parenteral exposure. The diagnosis of acute infection should be based on detection of HCV RNA by a sensitive technique. This testing can be performed at any time after the first week after exposure, but antiviral treatment is not an emergency in this setting and can be initiated after appearance of serum aminotransferase elevations or clinical symptoms appear.

Prognosis of HCV-Related Disease

No virologic test (including viral load and genotype) correlates with the severity of liver injury or fibrosis, or predicts the natural course or outcome of disease or presence of extra-hepatic disease. Virologic tests are not helpful as prognostic markers.

Antiviral Treatment of HCV Infection

Decision to treat. Only patients with detectable HCV RNA should be considered for treatment. HCV genotype determination should be performed before treatment as results may help in the decision to treat as well as in determining the duration of treatment. Thus, because of the high rates of response and need for 24 weeks of therapy only in patients with HCV genotypes 2 and 3, many investigators recommend therapy to all such patients provided there are no contraindications. Because response rates are only 40–45 percent and therapy must be given for 48 weeks in patients with genotype 1, the benefits of therapy must be balanced against its risks and cost. In this context, the assessment of the natural prognosis of infection by liver biopsy examination may help in making the decision to treat. In the absence of sufficient information, the same applies to genotypes 4, 5, and 6.

Virologic followup and assessment of response. Measurement of HCV RNA levels before treatment and again at 12 weeks has been proposed as an appropriate approach to monitoring patients with chronic hepatitis C who are treated with peginterferon and ribavirin. This is particularly true for patients with genotype 1. In patients infected with genotypes 2, 3, 4, 5, and 6, monitoring of HCV RNA levels may be less important, and there is little data supporting its usefulness. The basis for this will be discussed later in this conference. In all patients, however, the virological response should be assessed by testing for HCV RNA by a sensitive technique at the end of therapy. The presence of HCV RNA at the end of treatment is highly predictive of a relapse when therapy is stopped. The absence of HCV RNA at the end of

treatment indicates virological response and should lead to retesting for HCV RNA by a sensitive method 24 weeks later to document that the virological response is sustained.

Followup of Untreated Patients

Repeat virological testing is not necessary in untreated patients, as results have no prognostic value.

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Hepatocellular Carcinoma (HCC) and HCV in the United States

Hashem B. El-Serag, M.D., M.P.H.

HCC in the United States

A progressive increase in HCC-related mortality has been observed over the last 3 decades. According to the United States vital statistics, the overall age-adjusted mortality rate for HCC (ICD-9 155.0, which excludes cholangiocarcinoma and metastatic liver cancer) has risen significantly from 1.7 per 100,000 (95 percent CI, 1.7 to 1.8) during 1981–1995 to 2.4 per 100,000 (2.4 to 2.5) during 1991–1995. The recent rise in HCC mortality in the United States is a result of the rising incidence rate of HCC observed during the same time period coupled with a dismal survival rate (5 percent at 5 years). Data from the population-based SEER registries indicate that the age-adjusted incidence rate of HCC (ICD-O 8170) has increased from 1.4 per 100,000 during 1976–1980 to 3.0 per 100,000 during 1996–1998, more than a twofold increase. The latter rates probably underestimate the true incidence by approximately 30 percent as they represent only histologically confirmed HCC. During the same time, the temporal trends for hospitalizations with primary liver cancer have mirrored those of incidence and mortality. For example, data from the national VA computerized database show that the overall number of hospitalizations as well as the age-adjusted proportional hospitalization rate for HCC have increased by 42 percent from 1981–1997, reaching a hospitalization rate of 4.1 per 10,000 (3.7 to 4.5) during 1993–1997.

Demographic Risk Factors for HCC

There are significant gender, ethnicity, and geographic variations in the incidence of HCC in the United States. Caucasians are two to three times less affected than African Americans, who in turn are two to three times less affected than Asians, Pacific Islanders, or Native Americans. For all ethnic groups, men are two to three time more affected than women. Asians men have the highest age-adjusted incidence rates (up to 23 per 100,000). However, men and women of all ethnic groups have been affected by the recent increase in incidence. The reasons for these ethnic and gender variations probably relate to the prevalence and time of acquisition of the major HCC risk factors. It is known that the prevalence of HCV, HBV, and alcoholic cirrhosis is two- to threefold higher in African-Americans and Hispanics than in whites. Native American Eskimos and recent immigrants from China, Taiwan, Korea, and Vietnam have high prevalence rates of HBV similar to those in their original countries. There are significant geographic variations within the United States in HCC (irrespective of the demographic differences between these regions): Hawaii had the highest age-adjusted incidence rate (4.6/100,000), followed by San Francisco-Oakland (3.2/100,000) and New Mexico (2.0/100,000), whereas Iowa and Utah have the lowest rates of approximately 1.0/100,000.

We used hierarchical linear multivariate analysis to examine the temporal trends in HCC incidence while controlling for age, gender, and ethnicity as well as adjusting for potential

clustering of persons with similar demographic characteristics within geographic regions. **This analysis has confirmed a twofold increase in HCC over a time period between 1975 and 1998 while adjusting for all the variables described above**.

Concomitant with the rising rates of HCC, there has been a shift of incidence from typically elderly patients to relatively younger patients between ages 40 to 60. This shift reflects a cohort/period effect, affecting those who were born after 1920 and who seem to have been exposed to environmental agent(s) that have caused a cumulative increase in the HCC risk in all age groups of these cohorts. One plausible hypothesis is that these cohorts were infected with HCV during the 1950s–1970s, when they were in their twenties to forties, and are now presenting with HCV-related HCC. The full extent of this cohort/period effect has not been realized yet (the incidence rates have not leveled off yet).

Underlying Etiology for the Rising Incidence of HCC in the United States

Due to the essential role of cirrhosis in the development of HCC in the majority of cases, an increase in the number of persons living with cirrhosis is the likely explanation of the rising incidence of HCC. Declines in the mortality rates due to cirrhosis (partly related to improved management of esophageal varices and peritonitis) have been observed in the United States over the last 25 years. In addition, the incidence of cirrhosis related to HCV infection is rising. We carried out a population-based study in which the computerized records of hospitalized HCC patients during 1993 and 1998 (n=1,605) in all VA hospitals were searched for specific risk factors. There was a threefold increase in the age-adjusted rates for HCC associated with HCV from 2.3 per 100,000 (1.8 to 3.0) between 1993 and 1995 to 7.0 per 100,000 (5.9 to 8.1) between 1996 and 1998. HCV infection accounted for at least half of the increase in the number of HCC cases among United States veterans. During the same time periods, age-adjusted rates for HCC with either HBV (2.2 vs. 3.1 per 100,000) or alcoholic cirrhosis (8.4 vs. 9.1 per 100,000) remained stable. The rates for HCC without risk factors have also remained without a statistically significant change from 17.5 (15.8 to 19.1) between 1993 and 1995 to 19.0 per 100,000 (17.3 to 20.7) between 1996 and 1998. Thirty-eight percent of patients without specific risk factors had a diagnosis of nonspecific cirrhosis, many of whom were not tested for HCV. Similar trends have been observed from the large referral setting of M.D. Anderson Medical Center, where we recently reviewed the medical records of all patients residing in the United States who received a pathological diagnosis of HCC during 1993–1998; all patients were tested for HCV and HBV. The number of patients referred with HCC steadily increased from 143 in 1993–1995 to 216 in 1996–1998; of those, 26 patients (18 percent) and 66 patients (31 percent) were HCV positive during 1993–1995 and 1996–1998, respectively ($P = 0.01$). These data and a summary of all published HCC studies in the United States indicate that HCV is present in approximately 25–30 percent of cases, with more recent series reporting a greater proportion of HCV-related cirrhosis.

The risk of HCC in HCV: Cirrhosis is present in virtually all cases of HCV-related HCC. Once cirrhosis is established, HCC develops at an annual rate of 1 percent to 5 percent. The more important figure, the incidence of cirrhosis in HCV-infected patients, is more difficult to determine. We have examined the natural history of HCV (i.e., non-treated) in a systematic review of the literature among all subjects at risk for chronic HCV infection (excluding studies in

which cohorts were selected from patients with chronic liver disease and those where the onset time of infection could not be identified). The incidence rates of cirrhosis and HCC were determined in 21 studies. Even within this selected groups of studies, large variations were found in the estimates of cirrhosis (0–33 percent) and HCC (0–2.8 percent), time to cirrhosis (13–23 yrs), and time to HCC (17–31 yrs). Short duration of followup, small sample size, incomplete documentation of risk factors (e.g., alcohol), and incomplete screening for cirrhosis/HCC explain some of these variations. Due to the significant heterogeneity in these results, pooled estimates from studies are unlikely to be valid. Nevertheless, in studies with the best-documented onset of infection, there is an average incidence of cirrhosis of 1 percent per year and of HCC of 0.05 percent per year (20 percent and 1 percent at 20 years, respectively) in patients with chronic HCV infection. The mode of HCV acquisition appears to affect the progression of HCV; studies of community-acquired or Anti-D IgG related HCV infection had more benign course than that associated with transfusion or hemophilia. A graphic presentation of the incidence rates of cirrhosis or HCC vs. the sample size/duration of followup suggests the presence of publication bias and that the true estimates could be significantly higher or lower than those described above.

Host related factors seem to be more important than viral factors in determining the progression of HCV infection to cirrhosis and HCC. These factors include **older age of HCV acquisition**, **male gender (x2–3)**, **heavy alcohol intake > 50 gm/day (x5–50)**, **HBV (x 5–15) or HIV co-infection**, and possibly increased hepatic iron. Most important of all seems to be **time elapsed since acquiring HCV infection** with a median time of 30 years being the time frame when most HCC starts appearing. All HCV genotypes have been implicated in HCV-related HCC. **Diabetes and obesity** are also emerging risk factors; in a large case-control study among veterans (823 patients with HCC and 3,459 controls), we found diabetes to be associated with a 1.5-fold increase in the risk of HCC in the presence of other major HCC risk factors such as HCV, HBV, and alcoholic cirrhosis. Obesity has been shown to increase the risk of hepatic steatosis and fibrosis in HCV-infected patients, and diabetes is a known risk for NASH, which could progress to cirrhosis.

Due to the large pool of HCV-infected persons, it is likely that the rising incidence of HCC will continue over the next several years. Despite having a current HCV prevalence similar to that of Japan 20–30 years earlier, extrapolating the current Japanese HCC trends (10 times that of the current United States rates) to future trends in the United States may be inappropriate. (For example, <40 percent in the United States is HCV-related vs. 90 percent of HCC in Japan; also, most patients with end-stage liver disease in the United States die from non-HCC cirrhosis related complications, whereas in Japan, decompensated liver disease is unusual.)

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Screening for Hepatocellular Carcinoma (HCC): A Systematic Review

Kelly A. Gebo, Mollie W. Jenckes, Geetanjali Chander, Khalil G. Ghanem, H. Franklin Herlong, Michael Torbenson, Mark S. Sulkowski, Kirk A. Harris, Samer El-Kamary, and Eric B. Bass

Introduction

Hepatocellular carcinoma (HCC) is one of the most serious complications of chronic hepatitis C. For patients with chronic hepatitis C, practices of screening for HCC vary widely, largely because of uncertainty about the efficacy of screening tests in this population.

Objective

We conducted a systematic review of the literature to determine: (1) the performance characteristics of screening tests for HCC in patients with chronic hepatitis C (e.g., sensitivity, specificity); and (2) whether use of screening tests for HCC in patients with chronic hepatitis C can improve outcomes.

Methods

Literature Sources: Seven electronic databases were searched through DIALOG for the period from January 1996 to March 2002. Additional articles were identified by searching references in pertinent articles, hand searching relevant journals, and querying technical experts.

Eligibility Criteria: Exclusion criteria for review included: non-English language, articles limited to basic science or non-human data, previously reported data, and meeting abstracts.

Inclusion criteria for review were: study designed to address our key question, information pertinent to management of hepatitis C, and 30 or more study subjects with hepatitis C. In addition, we required histologic confirmation of at least 50 percent of the HCC cases for studies on performance characteristics of screening tests, and at least six months of followup for studies evaluating use of screening tests to improve outcomes.

Assessment of Study Quality: Each eligible article was reviewed by a pair of reviewers, including at least one team member with relevant clinical training and/or one with training in epidemiology and research methods. Paired reviewers independently rated the quality of each study in terms of the following categories: representativeness of study subjects (5 items); bias and confounding (4 items); description of therapy (4 items); outcomes and followup (5 items); statistical quality and interpretation (4 items). Reviewers assigned each response level a score of 0 (criterion not met), 1 (criterion partially met), or 2 (criterion fully met) to each relevant item on the quality form. The score for each category of study quality was the percentage of the total

points available in each category and therefore could range from 0–100 percent. The overall quality score was the average of the five categorical scores. We also documented source of funding.

Extraction of Data: The paired reviewers also abstracted data on type of study and geographical location; study groups; specific aims; inclusion and exclusion criteria; screening regimen; demographic, social, and clinical characteristics of subjects; and results. Differences between the two reviewers in either quality or content abstraction were resolved by consensus.

Synthesis

Results of Literature Search

We identified 3,104 potentially relevant citations, and 1,731 of these were eligible for abstract review. Through the abstract review process we identified 39 articles that could contain data on one of our key questions about screening for HCC in patients with chronic hepatitis C. After reviewing these 39 articles, we found 17 studies that answered question 1 regarding performance characteristics of the screening tests and one study that answered question 2 regarding outcomes with screening for HCC. Data from these eligible studies will be presented in a series of evidence tables and figures highlighting their distinguishing characteristics, methodologic strengths and limitations, and key findings.

Prevention of Spread of HCV

Miriam J. Alter, Ph.D.

Historically, the most reliable data on risk factors associated with acquiring hepatitis C virus (HCV) infection have been obtained from cohort (prospective) studies that determined the risk of developing acute infection after a specific exposure and case-control (retrospective) studies that determined if a history of exposure before onset of disease was associated with newly acquired (acute) hepatitis C. Risk factors identified by these studies in the United States included injecting drug use, blood transfusion and solid organ transplants from infected donors, occupational exposure to blood (primarily contaminated needle sticks), birth to an infected mother, sex with an infected partner, or multiple heterosexual partners.

The major limitation of such studies is that they are unlikely to identify associations with exposures that result only rarely in infections. For example, results of case-control studies have indicated no association between acquiring hepatitis C and exposures resulting from medical, surgical, or dental procedures. However, outbreaks of HCV infection have been associated with contaminated equipment in hemodialysis settings and unsafe injection practices in both inpatient and outpatient settings. Most of these outbreaks have involved patient-to-patient transmission. Only two instances of transmission have been reported from HCV-infected health care workers to patients in the United States. Neither of these was associated with the performance of exposure-prone invasive procedures, but rather with contamination of patients' narcotics used for self-injection.

The contribution of these various risk factors to the overall burden of HCV infections is influenced both by their efficiency in transmitting HCV and by the frequency of the exposure in the population. In the United States, the relative importance of the two most efficient exposures associated with transmission of HCV, blood transfusion and injecting drug use, has changed over time. Blood transfusion, which accounted for a substantial proportion of HCV infections acquired >15–20 years ago, rarely accounts for recently acquired infections. In contrast, injecting drug use consistently has accounted for a substantial proportion of HCV infections and currently accounts for 60 percent of HCV transmission. The relative importance of other exposures has changed little over time.

Unprotected sex with an infected partner or with multiple partners has accounted for an estimated 15 percent of HCV infections. Although the role of sexual activity in the transmission of HCV remains controversial, and the virus is inefficiently spread in this manner, the relatively substantial contribution of sexual exposures to the burden of disease can be explained by the fact that sexual activity with multiple partners is a common behavior in the population and that the large number of chronically infected persons provides multiple opportunities for exposure.

In contrast to sexual exposures, occupational and perinatal exposures contribute to a small proportion overall of infections, and together with nosocomial or iatrogenic exposures, they account for about 5 percent of HCV infections. HCV is not transmitted efficiently through occupational exposure. The prevalence of HCV infection among health care or public safety workers averages 1–3 percent and has not been affected by changes or improvements in barrier

precautions. Transmission rates from HCV infected mothers to their infants average 5 percent or less, no associations have been demonstrated with mode of delivery or type of feeding, and infants who acquire HCV infection at birth may be less likely to develop chronic infection.

Thus, about 90 percent of HCV infections can be accounted for by known percutaneous or mucosal exposures to blood. In the remaining 10 percent, no recognized source for infection can be identified. Numerous studies have attempted to identify additional risk factors for HCV infection. While case-control studies of acute hepatitis C reported no association with tattooing, acupuncture, ear piercing, military service, or foreign travel, cross-sectional and prevalence studies of volunteer blood donors, disease-specific clinic patients, and veterans receiving care in VA hospitals have yielded conflicting results for some of these risk factors. The lack of consistency among studies of highly selected groups for which the temporal sequence of exposure relative to the disease was unknown is cause for concern about the generalizability of such results.

Strategies for reducing or eliminating the potential risk for transmission include: (1) screening and testing of donors; (2) virus inactivation of plasma-derived products; (3) risk reduction counseling and services; and (4) implementation and maintenance of infection-control practices. Strategies for reducing risks for chronic disease include: (1) identification, counseling, and testing of at-risk persons; and (2) medical evaluation and management of infected persons.

Health care professionals in all patient care settings routinely should obtain a history that inquires about blood transfusion, use of illegal drugs (injection and non-injection) and evidence of high-risk sexual practices, such as multiple sex partners or history of STDs. Primary prevention of illegal drug injecting will eliminate the greatest risk factor for HCV infection in the United States. Although consistent data are lacking regarding the extent to which sexual activity contributes to HCV transmission, persons having multiple sex partners are at risk of STDs such as HIV, HBV, syphilis, gonorrhea, and chlamydia.

Testing should be offered routinely to persons most likely to be infected with HCV, which include persons who ever injected illegal drugs; received plasma-derived products known to transmit HCV infection that were not treated to inactivate viruses; received transfusions or solid organ transplants before July 1992; and were long-term hemodialysis patients. Based on a recognized exposure, testing also is indicated for health-care workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood and for children born to HCV-positive women. Immune globulin and antiviral agents are not recommended for postexposure prophylaxis of hepatitis C.

HCV-positive persons with a long-term steady partner do not need to change their sexual practices; however, they should discuss with their partner the need for counseling and testing, and the couple should be informed of available data on risk for sexual transmission of HCV to assist them in making decisions about precautions, including the low, but not absent, risk for transmission. HCV-positive persons do not need to avoid pregnancy or breastfeeding, and determining the need for cesarean delivery vs. vaginal delivery should not be made on the basis of HCV infection status. There are no recommendations for routine restriction of professional activities for HCV-infected health-care workers, and persons should not be excluded from work, school, play, child-care or other settings on the basis of their HCV infection status.

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Sexual Activity as a Risk Factor for Hepatitis C Infection

Norah A. Terrault, M.D., M.P.H.

Percutaneous exposures are well-recognized risk factors for HCV, hepatitis B virus (HBV), and HIV. However, there are clear differences between these viruses with respect to their frequency of transmission through sexual contact. The accumulated epidemiological evidence indicates that HCV can be sexually transmitted but much less efficiently than HBV and HIV.

Epidemiological studies evaluating the magnitude of risk of HCV transmission by sexual activity have several methodological shortcomings that tend to overestimate the proportion of HCV infections associated with sexual contact. Early studies used first-generation anti-HCV assays, which have a higher false positive rate than second- and third-generation assays. Studies vary in the completeness of risk ascertainment and many fail to carefully exclude HCV acquisition from non-sexual sources. Non-disclosure of injection drug use (IDU) as a risk factor is particularly important since assessing the contribution of sexual activity to HCV transmission is difficult in the presence of IDU. Finally, only a limited number of studies perform virological analyses to confirm that sexual partners are infected with the same virus and to exclude acquisition from outside sources.

Reported rates of HCV infection in sexual partners differ by geographical region, with higher rates reported in countries with higher endemic rates of HCV infection. Rates of anti-HCV positivity also vary by risk group, with higher rates of HCV reported in persons with a history of sexually transmitted diseases (STDs) and lower rates in heterosexual partners in long-term relationships. This difference may reflect the frequency of exposure to different HCV-infected sexual partners (higher in those with multiple partners than those in monogamous relationships). Alternatively, these risk groups may reflect differing rates of exposure to other non-sexual sources of HCV, such as IDU. The findings regarding sexual transmission in one group may not be generalizable to other groups or to the general population.

How Prevalent is the Risk Factor “Sexual Activity” in Persons With Acute Hepatitis C?

The Centers for Disease Control and Prevention collects detailed risk factor data on newly diagnosed cases of acute hepatitis C. In these surveillance studies, 15–20 percent of cases of acute community-acquired HCV occur in persons who report unprotected sexual contact with an anti-HCV positive person in the preceding 6-month period (two-thirds of cases) or multiple sexual partners (one-third of cases) as their only risk factor for HCV acquisition. Limited access to the sexual contacts prevents virological evaluation of the transmission events.

What is the Prevalence of HCV in Persons at Risk for Sexually Transmitted Diseases?

In U.S. seroprevalence studies conducted among sex workers, persons attending STD clinics, or persons participating in HIV surveillance studies, 1.6–25.5 percent of individuals are anti-HCV positive. In studies including persons with a history of IDU, anti-HCV positivity is more strongly associated with IDU than with factors related to sexual practices. In studies limited to individuals without a history of IDU, anti-HCV positivity is identified in 1.6–7 percent of STD clinic attendees, and risk factors associated with HCV are number of recent and lifetime partners, high-risk sexual contact (variably defined), and anti-HIV positivity. In homosexual and bisexual men, rates of anti-HCV positivity range from 2.9–12.7 percent with higher rates among those with HIV infection, but again IDU rather than sexual risk factors is most strongly associated with being HCV-positive.

What is the Prevalence of HCV in Monogamous Heterosexual Couples?

Among steady heterosexual partners of HCV-infected, HIV-negative persons, 0–24 percent are anti-HCV positive, with marked geographical variability. The median rate of anti-HCV positivity in sexual partners is 1.0 percent in North America and Northern Europe, 6 percent in Southern Europe, and 11 percent in Southeast Asia. Studies using genotyping or viral sequence analysis to assess anti-HCV concordant couples find lower rates of HCV transmission than studies using antibody testing alone. The duration of the sexual relationship is not predictive of HCV positivity in partners after adjusting for age. In studies comparing HCV positivity among sex partners vs. other family members, the rates of HCV positivity are higher in spouses than in other family members. However, after controlling for age and other parenteral exposures, anti-HCV positivity is no longer consistently associated with the type of relationship.

The majority of the published studies use genotyping rather than viral sequence analysis to evaluate anti-HCV concordant couples. Genotyping is suboptimal since HCV genotypes that are prevalent in the population may be present in partners even though they may have acquired the virus from different sources. For example, a study of 24 anti-HCV concordant couples found that 12 had concordant genotypes, 7 had discordant genotypes, and 5 were untypable. Seven of the 12 couples could be analyzed by sequence analysis, and only 3 were highly homologous and consistent with transmission. Thus, overestimation of HCV sexual transmission occurs if genotyping rather than sequence analyses is used to evaluate infected partners.

What is the Incidence of HCV Infection in "At Risk" Individuals?

In prospective studies (1–3.7 years followup) conducted in high-risk cohorts of non-IDU sex workers and patients in STD clinics, the incidence of HCV is 0.4–1.8/100 person-years (~1 percent). Small sample size precludes evaluation of specific sexual practices as risks for HCV acquisition. Undisclosed IDU may contribute the higher incidence of infection in this subgroup.

Based upon results from a prospective cohort of 499 Italian couples followed for a mean of 12.4 months, the incidence of new infection in sexual partners is 12 per 1,000 person-years.

Sequence analysis of the HCV-positive couples reveals a high degree of sequence homology in only 50 percent of the couples, suggesting non-sexual sources of HCV acquisition and a true incidence of no more than 6 per 1,000 person-years. In retrospective cohorts of female partners of hemophiliacs, the incidence is 1 to 1.87 per 1,000 person-years; among male partners of women infected by contaminated anti-D immunoglobulin, the incidence is 0.28 per 1,000 person-years; and among liver clinic patients and their sexual partners, the incidence is 1 to 3.86 per 1,000 person-years.

Factors That May Affect the Risk of HCV Transmission by Sexual Contact

In studies involving persons at risk for STDs, HIV co-infection is an independent predictor of anti-HCV positivity in the majority of studies. In studies involving hemophiliacs with HIV and HCV, the rate of anti-HCV positivity is higher in female partners of dually-infected men compared to men with HCV infection only. Studies from STD clinic attendees also suggest that co-infection with other STDs or sexual practices which may traumatize the mucosa (anal receptive sex) may increase the risk of sexual transmission of HCV. Whether the risk of HCV transmission differs for males vs. females is unclear. In one study of heterosexual couples in STD clinics, females with HCV-positive partners were 3.7 times more likely to have HCV than females with HCV-negative partners; this pattern was not evident in males. The titer of HCV RNA and HCV genotype do not appear to influence the risk of HCV transmission, but high-quality studies to assess these virological factors are lacking.

Summary

The available data indicate that HCV can be sexually transmitted but the efficiency of transmission by the sexual route is low. The risk of sexual transmission of HCV is estimated to be 0.03 percent to 0.6 percent per year for those in monogamous relationships, and 1 percent per year for those with multiple sexual partners.

Given these estimates of risk, the current recommendations are:

1. HCV-positive individuals in longer-term monogamous relationships need not change their sexual practices. If couples wish to reduce the already low risk of HCV transmission by sexual contact, barrier precautions may be used. Partners of HCV-positive persons should be considered for anti-HCV testing.

2. For HCV-infected individuals with multiple or short-term sexual partners, barrier methods or abstinence are recommended.

Additional common-sense recommendations include the use of barrier precautions if other STDs are present, if having sex during menses, or if engaging in sexual practices that might traumatize the genital mucosa. Finally, couples should not share personal items that may be contaminated by blood such as razors, toothbrushes, and nail-grooming equipment.

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Maternal-Infant Transmission

Eve A. Roberts, M.D., F.R.C.P.C.

With the advent of effective screening methods for hepatitis C virus (HCV), new cases of transfusion-associated hepatitis C have become infrequent in children. Consequently, childhood acquisition of HCV infection through maternal-infant transmission has assumed new importance. Vertical, or more precisely, mother-to-infant, hepatitis C will likely be the major type of childhood chronic hepatitis C within 6–8 years. It has been difficult to determine the rate of mother-to-infant transmission, partly because reports of mother-to-infant transmission of HCV were based on small numbers of patients, with differing disease definitions and study design. These reports tended to be heterogeneous and conflicting. Moreover, factors which promote mother-to-infant transmission and the outcome of chronic HCV infection acquired by this route still require clarification.

The first problem encountered with mother-to-infant transmission of HCV infection relates to its scope. Available estimates as to the prevalence of detectable anti-HCV among pregnant women range from 0.6 percent to 4.5 percent (median of 11 reports: 1.2 percent), with considerable geographic variation. Women with chronic hepatitis C appear to tolerate pregnancy as well as other women with non-cirrhotic chronic liver disease. Trivial improvement in serum aminotransferases may occur. Maternal viral titers may rise toward the end of the third trimester.

A second important problem is how exactly to define mother-to-infant transmission of HCV infection. Many infants of mothers chronically infected with HCV are found to have detectable anti-HCV in their blood, acquired through passive transplacental transfer of the IgG-antibody. This passively-acquired antibody continues to be detectable in the infant for the first 12–15 months of life, occasionally as long as the first 18 months. Possible criteria for a more rigorous definition of mother-to-infant transmission of HCV infection include: detectable anti-HCV in an infant who is more than 18 months old, detection of HCV RNA in an infant who is 3–6 months old, detection of HCV RNA in the infant on at least two occasions, finding elevated serum aminotransferases in the child, or confirming identical genotype between mother and child. A reasonable diagnostic approach in the infant is positive serum HCV RNA on two occasions 3–4 months apart after the infant is 2 months old and/or anti-HCV detected after the infant is 18 months old.

Reports detailing mother-to-infant transmission of HCV have been reviewed from time to time. We carried out a critical review of the world literature published between 1992 and 2001. For inclusion, each study was required to have at least 10 mother-infant pairs; language restrictions were largely avoided. Criteria used for identifying mother-to-infant transmission of infection were (1) anti-HCV detected in an infant over 1 year old or (2) HCV RNA detected at least once in an infant 18 months old or less. Studies using first-generation ELISA or RIBA techniques without confirmatory PCR testing were excluded. A weighted rate of incidence was used to adjust for sample size and variance. Seventy-seven studies were included for review: almost all of these were prospective cohort studies. The number of mother-infant pairs in each study ranged from 10 to 1,338. Taken altogether, 383 cases of mother-to-infant hepatitis C were identified. If the mother was known only to be anti-HCV positive, the weighted rate of mother-to-infant transmission was 1.7 percent (compared to a crude rate of number positive/number at risk = 5.6 percent). If the mother was known to be viremic, that is, HCV RNA positive, the

weighted rate of mother-to-infant transmission was 4.3 percent (crude rate = 8.1 percent). Geographic variation was apparent from these studies. In Italian studies with viremic mothers, the mother-to-infant transmission rate (weighted) was 5.6 percent, in similar Japanese studies, 6.9 percent, and in studies with viremic mothers from elsewhere, 3.1 percent. As previously shown, co-infection with the human immunodeficiency virus (HIV) greatly increased mother-to-infant transmission of HCV: weighted rates from these studies were 19.4 percent for HIV-positive mothers compared to 3.5 percent for HIV-negative mothers. In six studies examining the importance of previous or ongoing intravenous drug abuse (IVDU), a subset of anti-HCV positive mothers (where maternal viremia was not reported) at higher risk for transmission of HCV was identified: the weighted rate of transmission was 8.6 percent in mothers who were anti-HCV positive and IVDU, compared to 3.4 percent in anti-HCV positive mothers without known IVDU.

Findings in the most recent prospective studies are similar. In a study from Ireland of 314 infants born to 296 anti-HCV-positive women, the rate of mother-to-infant transmission was 3.5 percent (minimum rate)–6.4 percent (based on observed cases). No significant differences were found with spontaneous rupture of membranes, duration of membrane rupture, vaginal delivery or cesarean section, or evident fetal distress. Infants tended to be small for gestational age, but this could not be attributed solely to maternal chronic hepatitis C. In a study of 2447 HIV-negative pregnant women from Italy, 78 women were identified as anti-HCV positive and these mother-child pairs were monitored for 2 years; 60 women were found to be HCV RNA positive. Eight infants were identified as infected with HCV: thus the mother-to-infant transmission rate was 13.3 percent. At 2 years of age, only two infants were still positive for HCV RNA, and therefore the overall mother-to-infant transmission rate was put at 3.3 percent. Mother-to-infant transmission correlated with high maternal viral load.

The maternal viral titer appears to be an important determinant of probability of mother-to-infant transmission of HCV infection. The critical level appears to be 10^5–10^6 copies per ml. Not all studies show a clear correlation between maternal viral titer and vertical transmission: the timing of when the titer determination was performed may be a confounder. In one study, high maternal titers of HCV correlated with virus detectable in colostrum. Data are inadequate to assess whether viral genotype makes a difference to the rate of mother-to-infant HCV transmission.

Mode of delivery has been examined as a possible determinant of mother-to-infant transmission of HCV infection. In most studies suitable for evaluation the mode of delivery did not make an important difference to virus transmission. One study from Japan showed that vaginal delivery was associated with increased risk of mother-to-infant transmission of HCV compared to caesarean section when high viral load ($\geq 2.5 \times 10^6$ copies/mL) was present; however, maternal HIV status was not documented, and cesarean section operations were not classified as elective or emergency. Another study suggested that elective, but not emergency, cesarean section confers protection against mother-to-infant transmission. This study, however, was not stratified for HIV status. Anti-HCV positive mothers may be more likely to have cesarean section for reasons related to general obstetric management. Whether prolonged rupture of membranes prior to delivery enhances the mother-to-infant transmission rate remains uncertain. Use of fetal monitoring might be a risk factor for virus transmission but has not been investigated adequately.

Breastfeeding is generally not considered to be a risk factor for mother-to-infant transmission of HCV. In published studies the rate of transmission is nearly identical in breast-

or bottle-fed infants. Whether these studies are adequate is open to question since duration and exclusivity of breastfeeding are not routinely described in detail. The safety of breastfeeding operates on the assumption that traumatized or cracked nipples are not present.

The outcome of mother-to-infant hepatitis C requires clarification. Subtleties of disease course are relevant to this discussion. Some infants may have transient viremia without real infection. Other infants may have acute, self-limited infection which is clinically inapparent (very early spontaneous resolution). Data relating to these early patterns of mother-to-infant HCV exposure/disease are scanty, mainly because of reluctance to take repeated blood samples from apparently healthy infants. Thus, outcome of mother-to-infant transmission of HCV is usually considered in terms of evolution to chronic hepatitis C, with later spontaneous clearance of HCV infection or progressive chronic liver disease. Whether children are more likely to clear chronic HCV infection than adults and whether transfusion-associated chronic hepatitis in children runs a different clinical course from chronic hepatitis C acquired by mother-to-infant transmission remain unanswered questions currently being investigated.

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Introduction to Therapy of Hepatitis C

Karen L. Lindsay, M.D.

Since the 1997 NIH Consensus Development Conference: Management of Hepatitis C, several important advances have occurred which have significantly impacted therapy of hepatitis C, notably the availability of sensitive, specific, and standardized assays for identifying HCV RNA in the serum,[1] and the evaluation and FDA-approval of ribavirin and pegylated alpha interferon. The vast majority of treatment data has been collected in patients with chronic hepatitis C viral infection (HCV), clinically compensated liver disease due to HCV, elevated ALT or AST, no medical contraindication to treatment, and no other significant medical illness.

Therapeutic End Points

Sustained Virological Response

HCV RNA testing is conducted before, during, and at the end of treatment and 24 weeks later. It is now clear that *sustained virological response* (SVR), defined by the absence of detectable HCV RNA in the serum by RT-PCR at the end of treatment and 24 weeks after the end of treatment, is the optimal end point of therapy. Although a surrogate end point[2] (a biomarker intended to substitute for a clinical end point), SVR is associated with important clinical end points (characteristics that measure how a patient feels, functions, or survives). Marked improvements in health-related quality of life in patients with SVR has been demonstrated using standardized quality of life instruments[3]. The effects of SVR on survival of patients with chronic HCV have not yet been precisely measured because of the necessity for long-term followup and the inclusion of large numbers of untreated patients or treated patients without SVR. Evaluation of other clinical end points which are likely to be associated with survival [liver histology, recurrence of detectable viremia, residual HCV in the liver, development of hepatocellular carcinoma (HCC)] has been conducted. In patients with SVR, followup liver biopsies[4–6] taken 1–11 years after treatment demonstrate clear improvement in 89–100 percent, and serial serum HCV RNA testing[4,5,7] revealed a recurrence of viremia (*late virologic relapse*) in only 0–4 percent. A low likelihood of late virologic relapse is supported by a recent large study in 400 patients with SVR[8] in whom HCV RNA was detectable in only 2 percent of liver biopsies taken 24 weeks after the end of treatment. These observations strongly suggest that the absence of detectable serum HCV RNA measured 24 weeks after the end of treatment will be associated with improvement in how patients feel and function, resolution of liver injury and reduction in hepatic fibrosis, and a very low likelihood of recurrent HCV infection, all of which are highly likely to improve patient survival. And, in two large recent studies from Japan,[9,10] treatment with interferon was associated with a reduction in development of hepatocellular carcinoma which was more pronounced in patients with SVR. These and other long-term followup studies in progress will be extremely important in defining the effect of SVR on survival in years to come.

Since the Conference in 1997, large Phase III clinical trials in HCV patients naïve to treatment have demonstrated several major advancements in therapeutic agents. Lengthening the course of unmodified alpha interferon (α-IFN) monotherapy from 24 to 48 weeks, adding ribavirin to α-IFN for 24 or 48 weeks[11,12] and using pegylated alfa interferon (PEG IFN) compared to α-IFN for 48 weeks[13–15] increases the likelihood of SVR. And, in two recent large trials[16,17] in which ribavirin was given in combination with either PEG IFN or α-IFN, the overall rate of SVR was 54 percent and 56 percent with PEG IFN compared to 47 percent and 45 percent with α-IFN.

In these trials, multivariate analyses of baseline factors have identified several variables as being associated with the likelihood of SVR: HCV genotype other than 1, lower baseline viral load, lighter baseline weight or lower body surface area, younger age, absence of bridging fibrosis/cirrhosis, higher ALT quotient, and female sex. In several analyses, sex is no longer significant when weight is taken into account. Of these variables, viral genotype, HCV RNA level, and body weight are most strongly associated with SVR, but none of these factors singly or in combination are highly predictive of SVR. The patient's race, in particular, being an African-American, although not identified in multivariate analyses of these large trials, also appears to be potentially associated with response.[18] On-treatment factors have also been evaluated, and virologic response during the first 24 weeks of treatment has been identified as highly predictive of SVR.[17] In addition, the patient's ability to adhere to the regimen by taking 80 percent of the intended dose of the two therapeutic agents for at least 80 percent of the intended duration of treatment is also associated with higher SVR rates.[19] The optimal approach, therefore, is the initiation of a therapeutic trial and identification of the appropriate time for determination of virologic response (stopping rules). Further work is needed to understand and optimize adherence to therapy.

Virologic Response with Relapse

Virologic response with relapse is defined by the absence of detectable HCV RNA in the serum by RT-PCR at the end of treatment (virologic response) followed by subsequent detectability of HCV RNA in the 24 weeks after the end of treatment. In such patients, HCV is either present in the serum at levels too low for the assay to detect, or potentially sequestered in other compartments. The availability of more sensitive assays, such as TMA,[20] will be extremely useful in such patients. Future studies are needed to determine whether lengthening the course of treatment in patients with detectable serum HCV RNA using a more sensitive assay is associated with SVR.

Virologic Non-Response

Virologic non-response is defined as the presence of detectable HCV RNA at the end of treatment. In general, this category of patients treated with interferon-based therapy have been inadequately studied as regards the role of viral resistance, treatment adherence, and specific immunologic, environmental, genetic, or other factors which play a role.

Non-Virologic Therapeutic End Points

Biochemical response [the lowering of ALT to within the normal range at the end of treatment or at the end of treatment and for 24 weeks following treatment (sustained biochemical response)] continues to be evaluated in large trials, but there are few studies describing the long-term benefit of a sustained biochemical response in the absence of SVR. Although these studies suggest that long-term biochemical response is associated with a decreased frequency of hepatocellular carcinoma,[21–23] the groups are not controlled for baseline stage of fibrosis.

Histologic response or histologic improvement has been evaluated as a secondary end point in large, Phase III trials in which fixed-duration therapy was given. Comparing paired liver biopsies using standardized scoring systems, it is conventionally defined as at least a 2-point decrease from baseline biopsy in the inflammation score or in the total score or a 1-point decrease in the fibrosis score.[11–17]

The clinical value of a biochemical or histological response as a primary end point will be of great importance in ongoing and future treatment trials in patients for whom interferon-based therapy is contraindicated, those who cannot tolerate interferon treatment, or those whose infection does not virologically respond to interferon-based therapy. Long-term pegylated interferon therapy in virologic non-responders is being studied in several trials. Current and future studies using anti-inflammatory and anti-fibrotic agents will also assess these end points. And, in the future, these end points will be extremely important in studies using specific inhibitors of viral replication currently in development in order to determine the effects of ***virologic suppression*** as an end point of therapy.

Other Patient Populations

Large, definitive treatment trials have been conducted and reported in more than 10,000 adult patients with elevated aminotransferases, clinically compensated chronic liver disease due to HCV, and no other significant medical disorder. However, results from adequately designed and statistically powered studies of other patient populations (children, normal aminotransferases; decompensated liver disease; post-organ transplant; HIV co-infection; inherited blood disorders; renal disease; neuropsychiatric disorders; vascular disease; indigent, homeless, or substance-addicted) are not available. In order to determine the safety and effectiveness of HCV treatment in these populations, definitive trials need to be performed.

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Optimal Therapy of Hepatitis C

Adrian M. Di Bisceglie, M.D.

Considerable progress has been made in therapy since the last Consensus Development Conference on Management of Hepatitis C in 1997. Using the sustained virologic response (SVR) rate as the standard definition of beneficial outcome of therapy, different treatments can be compared in various categories of patients. The combination of interferon alfa-2b and ribavirin resulted in SVR rates of 31–35 percent after a 24-week course and 38–43 percent after a 48-week course of therapy.[1] The use of pegylated rather than standard interferon with ribavirin increased the response rate to 54–56 percent.[2,3]

The efficacy of two different formulations of peginterferon combined with ribavirin were assessed in two recent pivotal trials. The first of these compared two different doses of peginterferon alfa-2b plus ribavirin to standard interferon alfa-2b plus ribavirin for the initial treatment of chronic hepatitis C.[2] In the trial, 1,530 patients were randomized to receive either: (1) peginterferon alfa-2b (1.5 mcg weekly: higher dose) plus ribavirin (800 mg daily), (2) peginterferon alfa-2b (1.5 mcg weekly for 4 weeks followed by 0.5 mcg weekly: lower dose) plus ribavirin (1,000–1,200 mg daily), or (3) standard interferon alfa-2b (3 million units thrice weekly) plus ribavirin (1,000–1,200 mg daily). The treatment duration in all groups was 48 weeks. End-of-treatment virologic responses were achieved in 65 percent of patients treated with higher dose peginterferon, 56 percent treated with lower dose peginterferon, and 54 percent treated with standard interferon and ribavirin. Sustained virologic responses occurred in 54 percent of patients in the higher dose peginterferon group, 47 percent in the lower dose group, and 47 percent in the standard interferon group. Among patients treated with the higher dose of peginterferon, SVRs were significantly higher in patients infected with HCV genotype 2 or 3 (82 percent) than in those with genotype 1 (42 percent). The initial level of HCV RNA in serum also correlated with the SVR rates. Patients with high initial levels of HCV RNA, defined as greater than 2 million copies/ml, had significantly lower response rates than those with lower levels of virus (less than 2 million copies /ml) (42 percent vs. 78 percent). The degree of hepatic fibrosis had a lesser impact on the outcome of therapy: the SVR rate was 57 percent in those with no or minimal fibrosis compared to 44 percent among those with bridging hepatic fibrosis or cirrhosis.

A second recent large, randomized controlled trial compared peginterferon alfa-2a (180 μg weekly) plus ribavirin (1,000–1,200mg daily) to the same dose of peginterferon alfa-2a alone, or standard interferon alfa-2b (3 million units thrice weekly) plus ribavirin (1,000–1,200 mg daily) in 1,121 patients.[3] End-of-treatment virologic responses occurred in 69 percent of patients treated with peginterferon alfa-2a plus ribavirin, 59 percent with peginterferon alone, and only 52 percent with standard interferon and ribavirin. Sustained virologic response rates were 56 percent, 30 percent, and 45 percent, respectively. As in virtually all studies of antiviral therapy, HCV genotype was a strong predictor of SVR, which occurred in 46 percent of those with genotype 1 compared to 76 percent with genotypes 2 or 3 in the peginterferon plus ribavirin group.

Thus, two large pivotal trials have shown that the combination of peginterferon and ribavirin given for 48 weeks yields the highest rate of sustained response. While this may be the most effective regimen overall, it may not be optimal for all patients and in all situations. At issue is the optimal dose of peginterferon, the optimal dose of ribavirin, and the optimal duration of therapy.

In the large trial of peginterferon alfa-2b, two doses of peginterferon were compared, both based upon body weight.[2] While the higher dose yielded a better overall response rate, SVR rates for patients with genotypes 2 and 3 were similar with the higher and the lower peginterferon doses (82 percent vs 80 percent). In the trial of peginterferon alfa-2a, a single dose not adjusted to body weight (180 mcg weekly) was tested, based upon previous studies which identified this to be the most effective dose when given alone without ribavirin.[4] Yet, in all of these studies, dose modifications because of side effects were common, and it is, therefore, possible that lower doses of peginterferon are just as effective and perhaps better tolerated.

The optimal dose of ribavirin for use in combination with either form of peginterferon is also not clear. In the study of peginterferon alfa-2b, two doses were used: 800 mg of ribavirin per day with the higher dose of peginterferon alfa-2b was compared to the more standard dose of ribavirin of 1,000–1,200 mg daily (based on body weight) with the lower dose of peginterferon. Post-hoc analyses suggested that the 800 mg dose of ribavirin was suboptimal, in that response rates correlated with body weight, so that SVR rates increased as the ribavirin dose per kg body weight increased up to the highest rates, which were achieved at 13 mg/kg. Only the standard dose of ribavirin was used in the studies of peginterferon alfa-2a.[3] Clearly, the effects of these small differences in ribavirin doses need to be properly assessed in prospective controlled trials.

In both of the pivotal trials of peginterferon, therapy was given for 48 weeks. Thus, the relative efficacies of shorter or longer courses are not known. A full 48 weeks of therapy is clearly not needed to achieve SVR in all patients. Evidence from earlier studies of standard interferon with ribavirin suggested that 24 weeks of therapy was sufficient for patients with genotypes 2 or 3 and in patients with genotype 1 and low levels of HCV RNA.[1] Furthermore, sequential testing for HCV RNA levels suggests that patients who do not respond can be identified as early as 24 or even 12 weeks of therapy;[2,3] if so, their therapy could be curtailed early, thus minimizing side effects and cost. Future studies are needed to assess the optimal duration of therapy in different categories of patients as well as to assess the possible role of sequential measurements of HCV RNA levels as a means of determining the optimal duration of treatment.

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Retreatment of Patients With Chronic Hepatitis C

Mitchell L. Shiffman, M.D.

A large number of patients with chronic hepatitis C have been treated with alpha interferon with or without ribavirin since the 1997 Consensus Development Conference. Unfortunately, a majority of these patients probably did not achieve a sustained virologic response (SVR). As new therapies are developed for hepatitis C, the issue of retreatment of these non-responders will continue to arise. Recommendations regarding retreatment should be based upon several factors: (1) the previous type of response, (2) the previous therapy and the difference in potency of the new therapy, (3) the severity of the underlying liver disease, (4) viral genotype and other predictive factors for response, and finally (5) tolerance of previous therapy and compliance.[1]

Types of Non-Response

Patients who fail to achieve SVR can be categorized as either relapsers or non-responders. In general, relapsers are more likely to achieve SVR during retreatment with a more potent regimen than are non-responders. Yet among patients referred to as non-responders, there is the subset who have a marked reduction without disappearance of HCV RNA (1–2 log units or more) during therapy. These partial responders may also be good candidates for retreatment, if a more potent regimen of therapy is being applied, such as the currently recommended combination of peginterferon and ribavirin. In at least one study of retreatment, only non-responders who had a decline in HCV RNA to an absolute titer <100,000 copies/ml during previous treatment with interferon alone achieved SVR when retreated with interferon and ribavirin.[2]

Retreatment of Non-Responders

The likelihood that non-responder patients will respond to retreatment depends in large part upon the previous therapy. Retreatment of non-responders with the same therapy will not result in viral clearance, whereas retreatment with a more potent regimen can result in SVR in a proportion of patients. Thus, preliminary results suggest that up to 30 percent of non-responders to the standard interferon/ribavirin combination became HCV RNA negative on retreatment using the peginterferon/ribavirin combination.[3,4] Higher rates occurred in patients with HCV genotypes 2 or 3 compared to genotype 1. Unfortunately, relapse was common once therapy was discontinued, so that the rate of SVR was only 15–20 percent overall.

Retreatment of Relapsers

Several studies have shown that patients with prior relapse have a high rate of SVR when retreated with more effective therapy. Thus, 50 percent of patients who relapsed following treatment with interferon alone achieved SVR when retreated with interferon/ribavirin combination.[5] The ability to achieve SVR following retreatment with peginterferon/ribavirin in

patients who relapsed following interferon monotherapy or standard interferon/ribavirin therapy is currently being evaluated. The majority of relapsers become HCV RNA negative during retreatment, even when the regimen is the same. When the same regimen is used, however, virtually all patients relapse again after treatment is stopped. Extending the duration of retreatment without changing the dose or regimen may reduce relapse, but this has not been prospectively proven.

Severity of Liver Disease and Retreatment

Knowledge of the severity of the underlying liver disease is important in recommending retreatment of chronic hepatitis C. Patients with no or minimal fibrosis probably have an excellent long-term prognosis and low risk for developing cirrhosis or complications of chronic hepatitis C. These patients, therefore, could forgo retreatment and await further advances in therapy. On the other hand, patients with advanced fibrosis or cirrhosis are at increased risk for developing hepatic decompensation and should be considered for retreatment, especially if the previous treatment was interferon alone. For patients with intermediate degrees of fibrosis and disease activity, recommendations for retreatment should weigh the type of initial response, the improvement in treatment regimen, factors such viral genotype, initial titer of HCV RNA, as well as tolerance of therapy.

Non-Responders to Combination Therapy With Peginterferon and Ribavirin

Patients who fail to respond even to the current optimal therapy with peginterferon/ ribavirin are a great challenge for management, particularly those with advanced fibrosis or cirrhosis. In several studies of standard interferon, up to 40 percent of non-responders developed evidence of a histological response despite persistence of HCV RNA.[6,7] These histological responses occurred largely among patients with a partial virological response as shown by a significant reduction in HCV RNA titer. In a prospective, randomized controlled trial, these histological improvements were shown to be maintained by continuation of interferon monotherapy.[8] The possible role of maintenance therapy with peginterferon alone in preventing further progression of cirrhosis, clinical decompensation, or development of hepatocellular carcinoma is currently the focus of a large-scale, multi-center U.S. trial, referred to as HALT-C. Until the results of that study or similar studies are available, the role of long-term, continuous therapy with peginterferon (or ribavirin or both) for non-responder patients must be considered experimental.

Tolerance and Compliance

An important reason for relapse and non-response to interferon therapy of hepatitis C is non-compliance. Non-compliance can be the result of severe side effects or lack of commitment by the patient, but also can be due to poor counseling regarding side effects and inadequate management. If the causes of non-compliance can be corrected or lessened, retreatment can be successful. In contrast, if side effects are intolerable despite adequate counseling and management, retreatment is unlikely to be successful and should not be encouraged.

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Treatment for Hepatitis C: A Systematic Review

Geetanjali Chander, Mark S. Sulkowski, Mollie W. Jenckes, Kelly A. Gebo, Khalil G. Ghanem, H. Franklin Herlong, Michael Torbenson, Kirk A. Harris, Samer El-Kamary, and Eric B. Bass

Introduction

Hepatitis C is a spherical enveloped RNA virus of the *Flaviviridae* family, which has been recognized as a major cause of chronic hepatitis and hepatic fibrosis that progresses in some patients to cirrhosis and hepatocellular carcinoma (HCC). In the United States, approximately 4 million people have been infected with hepatitis C (HCV) and 10,000 HCV-related deaths occur each year. Effective treatment strategies are needed to prevent hepatitis C-related morbidity and mortality.

Objective

We conducted a systematic review of the literature to determine: (1) the extent to which randomized controlled trials have shown the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients, including: pegylated interferon plus ribavirin; pegylated interferon alone; interferon plus ribavirin; and interferon plus amantadine; (2) the extent to which randomized controlled trials have shown 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 vs. decompensated liver disease, concurrent hepatitis B or HIV infection, non-response to initial interferon based therapy, and relapse after initial interferon based therapy; and (3) the long-term outcomes of current treatment options for chronic hepatitis C infection.

Methods

Literature Sources

Seven electronic databases were searched through DIALOG for the period from January 1996 to March 2002. Additional articles were identified by searching references in pertinent articles, hand searching relevant journals, and querying technical experts.

Eligibility Criteria

Exclusion criteria for review included: non-English language, articles limited to basic science or non-human data, previously reported data, and meeting abstracts.

Inclusion criteria for review were: study designed to address our key question, information pertinent to management of hepatitis C, and 30 or more study subjects with hepatitis C. In addition, treatment articles reviewed were limited to randomized controlled trials. To explore modern treatment options, we limited eligible studies to those evaluating interferon alone or in combination with other treatment options, e.g., ribavirin, amantadine, etc., *and* where outcomes were assessed by virologic and/or histologic measures of outcomes. Studies of interferon alone were only included when the study participants were subgroups of interest, e.g., renal disease, HIV co-infection. Studies evaluating long-term followup could be either randomized controlled trials or cohorts but required at least 60 months of observation.

Assessment of Study Quality

Each eligible article was reviewed by a pair of reviewers, including at least one team member with relevant clinical training and/or one with training in epidemiology and research methods. Paired reviewers independently rated the quality of each study in terms of the following categories: representativeness of study subjects (5 items); bias and confounding (4 items); description of therapy (4 items); outcomes and followup (5 items); statistical quality and interpretation (4 items). Reviewers assigned each response level a score of 0 (criterion not met), 1 (criterion partially met), or 2 (criterion fully met) to each relevant item on the quality form. The score for each category of study quality was the percentage of the total points available in each category and therefore could range from 0–100 percent. The overall quality score was the average of the five categorical scores. We also documented source of funding.

Extraction of Data

The paired reviewers also abstracted data on type of study and geographical location; study groups; specific aims; inclusion and exclusion criteria, screening regimen; demographic, social and clinical characteristics of subjects, and results. Differences between the two reviewers in either quality or content abstraction were resolved by consensus.

Synthesis

Results of Literature Search

We identified 3,104 potentially relevant citations and 1,731 of these were deemed eligible for abstract review. Through the abstract review process, we identified 486 articles that could have been related to one of our key questions regarding treatment. After reviewing these 486 articles, we found 231 studies including 165 randomized controlled trials reporting on current treatment and 66 reporting on long-term outcomes. Data from these eligible studies will be presented in a series of evidence tables and figures highlighting their distinguishing characteristics, methodologic strengths and limitations, and key findings.

Utilization of Virologic Testing in the Treatment of Chronic Hepatitis C

Gary L. Davis, M.D.

Slightly fewer than half of patients with chronic hepatitis C fail to eradicate hepatitis C virus (HCV) when treated with the current regimen of combination therapy with pegylated interferon and oral ribavirin (PEG-R).[1,2] With past treatment regimens including interferon monotherapy or the combination of standard interferon with ribavirin, patients who remained HCV RNA positive by qualitative testing by RT-PCR after 12 or 24 weeks, respectively, had little or no chance of achieving a sustained virologic response (SVR).[3,4] Preliminary data from one of the PEG-R studies suggested that the most appropriate timepoint for assessing response with the current regimen was also 24 weeks.[1]. Thus, treatment could be discontinued early in viral non-responders, saving them the inconvenience and expense of the latter half of the treatment course. However, several papers also reported that the lack of an even earlier reduction in viral level was predictive of non-response despite continued treatment.[5,6] Unfortunately, these reports examined small numbers of patients and used quantitative assays for HCV RNA that were neither reliable or commercially available. Recently, several standardized commercially assays for quantitating HCV RNA have become available. The role of these quantitative tests in assessing early virologic response (or non-response) to PEG-R has not been studied.

The goal of the current analysis was to determine whether reduction of the level of HCV RNA during the first weeks of PEG-R treatment predicted response and non-response at the end of treatment and whether this information would be used to formulate early stopping rules before 24 weeks of treatment. Data from two recent large international clinical studies of pegylated interferon plus oral ribavirin was made available by the study sponsors, Schering Plough and Roche Pharmaceuticals, after agreement of the study investigators.[1,2] Only those treatment groups receiving the optimal regimen were included (PEG-IFNα2a 180 μg qwk + ribavirin 1000–1200 mg daily; PEG-IFNα2b 1.5 μg/kg qwk + ribavirin 800 mg daily). Quantitative HCV RNA was measured at baseline, 4 weeks, 12 weeks, and 24 weeks by the NGI method (Schering study) or Amplicor with appropriate dilutions of high titer samples (Roche study).[7,8] This data was analyzed to answer the following questions: (a) Can serial quantitative HCV RNA testing predict a lack of virologic response to PEG-R? (b) Can serial quantitative HCV RNA testing predict a sustained virologic response to PEG-R? (c) What is the optimal time to determine early virologic response?

The analysis of the 2 data sets with respect to the ability of the week 12 viral response to predict non-response is shown in Table 1. The results with the 2 different interferon regimens are nearly identical. Early virologic response (EVR) was best defined as a fall in HCV RNA level after the first 12 weeks of treatment to less than the lower limit of detection (PCR) or by at least 2 logs compared to the pre-treatment level. Overall, 82.7 percent of patients treated with this combination achieved EVR and 68 percent of these cases eventually achieved SVR. SVR was more than 50 percent more likely to occur in patients who were able to receive at least 80 percent of the recommended dose and duration of drugs. Failure to achieve an early virologic response

was highly predictive of non-response; only 2 of 161 (1.2 percent) patients without EVR ultimately achieved SVR. Viral response at 4 weeks was less predictive than the 12 week response; failure to achieve a 4 week EVR was associated with a 4 percent chance of SVR. A quantitative cutoff of more than 2 logs (e.g. 3 logs) missed some patients who ultimately achieved SVR while a less rigorous cutoff (e.g. 1 log) allowed too many non-responders to continue on treatment.

Table 1.

Early Virological Response	Treatment Response	
	SVR	NR
Study #1		
Yes	71.8%	28.2%
No	0.0%	100.0%
Study #2		
Yes	64.9%	35.1%
No	3.2%	96.8%
Combined Data		
Yes	68.3%	31.7%
No	1.2%	98.8%

In summary, most patients who receive treatment with pegylated interferon and ribavirin achieve early virologic response, defined as a fall in HCV RNA level by at least 2 logs or to undetectable by PCR after the first 12 weeks of treatment. About two-thirds of these patients will ultimately achieve SVR, thus providing excellent motivation to continue therapy and not dose reduce unnecessarily. In contrast, those who fail to achieve an early virologic response have only a very small chance of achieving SVR even if therapy is continued for a full year. Discontinuation of therapy is encouraged in these cases.

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The Role of Liver Biopsy in Therapy of Chronic Hepatitis C

Jules L. Dienstag, M.D.

As the efficacy of therapy for chronic hepatitis C improves, as acceptance of such therapy becomes more widespread, and as management of chronic hepatitis C extends from specialist hepatologists to nonspecialists, the role of liver biopsy in the management of chronic hepatitis C is being re-examined. When the role of liver biopsy was considered during the previous NIH Consensus Development Conference in 1997, pretreatment liver biopsy was endorsed as the "gold standard" for assessing the grade of liver injury and the stage of liver fibrosis in anticipation of antiviral therapy. The same recommendations appear in the consensus statement of the European Association for the Study of Liver Disease; are supported by the Centers for Disease Control, United States Public Health Service; and are implied in the consensus statement on prevention and management of hepatitis C in the Asia-Pacific region. Since that time, a series of reports have appeared either supporting or challenging the role of such histologic assessment in the management of chronic hepatitis C. In reevaluation of the value of liver biopsy, we should consider whether hepatic histology (a) provides prognostic information about the future natural history of chronic hepatitis C, (b) predicts the likelihood of response to antiviral therapy, and (c) remains the gold standard that it represented or can be supplanted by "surrogate" indicators.

Selecting patients for treatment would be easier if available therapy were uncomplicated, highly effective, simple to administer, limited in duration, and well tolerated. In patients with chronic hepatitis C, however, available therapy is far from ideal, and many factors color the decisions of individual patients and their physicians. Antiviral therapy for chronic hepatitis C requires injection therapy; side effects are common and especially difficult to accept in a population of predominantly asymptomatic persons; approximately half of treated patients fail to respond to the best therapy available; for many patients progression is so slow and limited that the decision to treat is readily postponed; and, if the steady progress in efficacy of antiviral therapy over the last decade is an indication of progress to come, many patients might fare just as well to wait until antiviral therapy improves. Perhaps, for patients with HCV genotypes 2 and 3, response to therapy is so likely that the threshold for treatment is achieved in almost all cases; however, because most patients have genotype 1, and because 60 percent of patients in this category fail to respond, pretreatment variables that shed light upon prognosis and likelihood of response to therapy are valuable for decision-making about therapy.

Although much is known about the natural history of chronic hepatitis C in large cohorts of affected persons, predicting the future course of the disease in any individual is difficult. Of the several potential prognostic variables, the most reliable appears to be histologic grade and stage, as assessed by one of several extant histologic classifications systems. Studies relying on serial liver biopsies suggest that patients with mild hepatitis and limited fibrosis progress slowly or not at all over a 10–20 year horizon, while those with moderate to severe inflammation (grade) and fibrosis (stage) progress inevitably to cirrhosis over a 20–10 year horizon, respectively. Therefore, a baseline biopsy is useful for determining the urgency of initiating therapy. Moreover, almost all instances of hepatitis C being discovered in clinical practice now represent hepatitis C virus (HCV) infections acquired one to three decades earlier, originating at a time of life when "risky" behavior occurred, even transiently. Thus, for most patients

undergoing liver biopsy for chronic hepatitis C, current biopsy includes an approximate assessment of the impact on inflammation and fibrosis of several decades of HCV infection and virus-associated liver injury. These observations have been invoked as the primary justification for recommending liver biopsy prior to embarking upon a course of antiviral therapy.

Liver biopsy is felt to be helpful in excluding other causes of liver injury that might confound interpretation of the clinical and histologic expression of HCV infection. Because some patients with chronic hepatitis C have other, concomitant causes of liver injury, a pretreatment liver biopsy to exclude such alternative factors as fat, alcohol, iron, etc. may shift clinical focus away from hepatitis C to the alternative process. Moreover, some of these factors, e.g., fat or iron, have been suggested to be cofactors in the progression of fibrosis. Another argument in favor of a pretreatment biopsy in patients with chronic hepatitis C can be made for anyone with any type of liver disorder for which treatment is an option. That is, a baseline biopsy obtained prior to committing a patient to long-term treatment preserves the value of potential subsequent histologic assessment for management decisions made in the future.

Based upon histologic prognostication, many clinicians decline to pursue therapy in patients with mild chronic hepatitis C. From a societal perspective, however, Wong et al. suggested that treatment of mild chronic hepatitis with combination interferon-ribavirin is actually cost-effective, reduces the risk of cirrhosis, and prolongs survival. The comparison strategy for this analysis was watchful waiting, with liver biopsies repeated every three years and therapy introduced for histologic progression; in addition, the calculated costs of therapy involved the combination of standard interferon with ribavirin. Although sensitivity analyses were included to address uncertainties in the many estimates required for such an analysis, this analysis was based upon costs of a previous generation of therapy, not the increased costs of contemporary therapy with pegylated interferon plus ribavirin. In addition, the benefit identified would be marginal or negligible if only one additional liver biopsy were to be performed in the future, and the analysis could not include the impact of the inevitable introduction of more effective, better tolerated treatments that would justify postponing treatment for several years. Whether critiques of this analysis are substantial or quibbling, the perspective of individual patients and physicians may be very different and no less valid or compelling than the societal perspective adopted in this analysis. For many patients with mild disease and a likelihood of progression to cirrhosis that may be as low as 20 percent over 20 years, a viable strategy would allow postponing treatment for several years and embracing therapy without an additional liver biopsy when more highly effective treatments become available.

Liver biopsy would be less important were other clinical or laboratory tests available that could predict reliably the grade of inflammatory injury or the stage of fibrosis; however, to date, no such surrogates have been validated. Weighing against liver biopsies are the high costs of the procedure as well as its invasive nature and associated risks. Because most patients referred for evaluation have moderate to severe chronic hepatitis on liver biopsy, and because liver biopsies have been found by some investigators to have a limited impact on decision-making about treatment, the importance of a pretreatment liver biopsy might be questioned. Even the assumption that liver biopsy would be valuable for excluding other diagnoses in patients with chronic hepatitis C could not be confirmed by Saadeh et al. Nevertheless, these investigators marshaled data to support the utility of pretreatment liver biopsy by showing limited sensitivity and specificity of nonhistologic approaches, none of which was adequately predictive of

histologic findings in the large majority of patients. Predicting the presence of cirrhosis is especially challenging; cirrhosis can be present in up to half of well compensated patients with chronic hepatitis C, and neither a single test nor a combination of clinical and laboratory features has been shown to have sufficient predictive value for the presence of cirrhosis. Given the implications of cirrhosis for surveillance and management, baseline biopsy takes on special importance.

On the other side of the coin, baseline biopsies have been reported to demonstrate unexpectedly mild liver disease in some patients referred for treatment, including persons with hemophilia and with injection drug use, and the more publicized women who received contaminated anti-D immune globulin in Ireland and Germany. Thus, nonhistologic assessments have neither the sensitivity nor the specificity to replace liver biopsy in the initial assessment of suitability for treatment.

Another area of potential controversy is the subset of patients with chronic hepatitis C but persistently normal aminotransferase activities. Anecdotal reports have appeared to show that some of these patients have histologically very severe or advanced liver disease, suggesting that all such patients require liver biopsy to unearth clinically subtle but advanced liver disease. When group data are evaluated, however, the preponderance of evidence suggests that severe liver injury is the marked exception in such patients. Moreover, among patients with chronic hepatitis C and persistently normal aminotransferase levels, histologic activity, as monitored by sequential liver biopsies over more than half a decade, does not progress. Therefore, and because the last NIH Consensus Development Conference in 1997 failed to identify any benefit of therapy in this subgroup, many authorities are reluctant to pursue liver biopsy in patients with normal aminotransferase activity.

Although other predictors of responsiveness to therapy exist, the degree of fibrosis has also been shown to be an independent inverse predictor of response to therapy. On the other hand, the negative predictive value of fibrosis or cirrhosis is too low to justify withholding therapy, and the need for therapy may be more compelling in this group of patients who have more advanced disease.

For contemporary antiviral therapy of chronic hepatitis C, pretreatment liver biopsy provides important information about prognosis and the need for early treatment and should be retained. Future research should focus on delineating how broadly histologic assessment should be implemented and whether other clinical features suffice to supplant liver biopsy under certain circumstances. Because liver biopsy is invasive, the search for noninvasive laboratory markers of necroinflammatory activity, fibrosis, and cirrhosis should command a high priority, as should the quest for genetic markers associated with accelerated disease progression.

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Utility of Liver Biopsy in Management of Hepatitis C: A Systematic Review

Khalil G. Ghanem, Michael Torbenson, Mollie W. Jenckes, Kelly A. Gebo, Geetanjali Chander, Mark S. Sulkowski, Kirk A. Harris, Samer El-Kamary, Eric B. Bass, and H. Franklin Herlong

Introduction

Liver biopsies are frequently recommended in the management of patients with chronic hepatitis C. Histologic criteria have been established to assess the severity of both inflammation and fibrosis. However, it remains uncertain how this information assists in establishing prognosis or predicting efficacy of treatment.

Objective

We conducted a systematic review of the literature to determine: (1) how the results of initial liver biopsy relate to measures of disease progression and treatment outcome as assessed by histologic and virologic parameters and (2) the value of serum biochemistry tests and serologic measures of fibrosis in predicting histologic findings.

Methods

Literature Sources

Seven electronic databases were searched through DIALOG for the period from January 1996 to March 2002. Additional articles were identified by searching references in pertinent articles, hand searching relevant journals, and querying technical experts.

Eligibility Criteria

Exclusion criteria for review included: non-English language, articles limited to basic science or non-human data, previously reported data, and meeting abstracts.

Inclusion criteria for review were: study designed to address our key question, information pertinent to management of hepatitis C, and 30 or more study subjects with hepatitis C. In addition, for those studies pertaining to how results of initial liver biopsy relate to measures of disease progression and treatment outcome, we required at least six months of followup after initial biopsy and outcomes measured by an appropriate objective standard such as virologic or histologic measures.

Assessment of Study Quality

Each eligible article was reviewed by a pair of reviewers, including at least one team member with relevant clinical training and/or one with training in epidemiology and research methods. Paired reviewers independently rated the quality of each study in terms of the following categories: representativeness of study subjects (5 items); bias and confounding (4 items); description of therapy (4 items); outcomes and followup (5 items); statistical quality and interpretation (4 items). Reviewers assigned each response level a score of 0 (criterion not met), 1 (criterion partially met), or 2 (criterion fully met) to each relevant item on the quality form. The score for each category of study quality was the percentage of the total points available in each category and therefore could range from 0–100 percent. The overall quality score was the average of the five categorical scores. We also documented source of funding.

Extraction of Data

The paired reviewers also abstracted data on type of study and geographical location; the study groups; specific aims; the inclusion and exclusion criteria; demographic, social, and clinical characteristics of subjects; and results. Differences between the two reviewers in either quality or content abstraction were resolved by consensus.

Synthesis

Results of Literature Search

We identified 3,104 potentially relevant citations and 1,731 of these were eligible for abstract review. Through the abstract review process we identified 254 articles that could contain data on one of our key questions regarding the utility of liver biopsy in patients with chronic hepatitis C. After reviewing these 254 articles, we found 147 studies that addressed the value of initial or followup biopsies predicting treatment outcomes and 107 articles that addressed the relationship between serological markers and histological findings. We subsequently reviewed the full articles to ensure they met our eligibility criteria. We have focused on randomized controlled trials of therapies for which assignment to a treatment was *not* determined by biopsy results. Data from these eligible studies will be presented in a series of evidence tables and figures highlighting their distinguishing characteristics, methodologic strengths and limitations, and key findings.

Children With Hepatitis C

Maureen M. Jonas, M.D.

Less is known about HCV infection in children compared to infection in adults, due to the small proportion of HCV-infected individuals that are children and the lack of manifestations of this infection during childhood. Nonetheless, most HCV-infected children develop chronic hepatitis, and, although rare, cirrhosis and end-stage liver disease have been described. There are differences in modes of acquisition, natural history, complications, and treatment between pediatric and adult HCV infection.

The seroprevalence of anti-HCV is 0.2 percent in children less than 12 years of age, and 0.4 percent in those 12 to 19 years of age. Using these figures, it can be estimated that there are somewhere around 240,000 exposed or infected children in this country. Although there has been a significant decrease in the incidence of new HCV infections in adults, new infections continue to occur in children via perinatal transmission. Because receipt of blood or blood products prior to 1992 was an important mode of transmission of HCV to children, there is a cohort of adolescents who have had HCV for 10–20 years. Perinatal transmission provides a cohort of infected children from newborns through the teenage years. Horizontal transmission, from adult to child in the household, or child-to-child at home or at school, does not seem to be an important factor in the epidemiology. The prevalence of HCV infection in children not currently explained by risk factors, i.e., sporadic or community-acquired HCV, is felt to be low. Many children infected with HCV are yet to be identified.

Acute HCV infection is rarely recognized in children, outside of special circumstances like a transfusion-associated outbreak. Fulminant hepatitis due to HCV has not been described in children. Chronically infected children are asymptomatic or have non-specific fatigue and/or abdominal pain, with normal or mildly abnormal ALT levels. Clinically apparent autoimmune manifestations are rare.

Independent effects of age at acquisition and mode of acquisition on natural history are difficult to separate in pediatric studies. In addition, the natural history of transfusion-associated HCV infection may differ according to the underlying disease for which transfusion is required. Some children who were transfused at the time of surgery for congenital heart disease developed chronic hepatitis, but others cleared the infection. Secondary hemochromatosis may contribute to the hepatic injury in children with thalassemia, and may mitigate the response to therapy in this group. Children treated for leukemia prior to 1990 have a very high rate of HCV infection, but in one cohort prolonged followup (13–27 years) did not commonly reveal serious liver disease. In contrast, an American study of individuals treated for childhood cancer revealed one death from liver disease and two deaths due to hepatocellular carcinoma in the decades following HCV acquisition. The same report described 3 (9 percent) cases of cirrhosis 9–27 years after diagnosis of the primary malignancy. Clearly, some cases of HCV infection acquired in childhood by transfusion are associated with serious liver disease in the decades following infection.

Whether the natural history of infection acquired perinatally is different from HCV acquired by transfusion is not yet clear. Vertically infected infants typically have elevated

alanine aminotransferase (ALT) levels for a few years, and those levels often become normal. Virtually all children who undergo liver biopsy have histologic chronic hepatitis. Thus it appears that HCV infection acquired vertically is frequently associated with biochemical evidence of hepatic injury early in life, persists in the majority, but not all, instances, and causes only mild liver disease in the first decades. However, in some children the infection takes an aggressive course leading to cirrhosis and even end-stage liver disease during childhood; the factors responsible for this are as yet unidentified.

There are no reports of treatment of acute HCV infection in children; acute infection is rarely recognized. In addition, no large, multicenter, randomized, controlled therapeutic trials have been performed in children with chronic HCV infection. Studies of treatment in children are most often uncontrolled, include small numbers of patients, and sometimes include only select patient groups, such as hemophiliacs or individuals with thalassemia. Details of the interferon monotherapy trials in children with chronic HCV infection were recently reviewed: even though the studies included several types of patients and used different dosages, schedules, and types of interferon, in general the sustained virologic response (SVR) rate was remarkably similar in most studies, ranging from 33–45 percent. This is significantly higher than the SVR rates reported in large trials of interferon monotherapy in adult patients. An analysis of these heterogeneous studies that included 11 manuscripts and 3 abstracts (in total included 270 treated children and 37 control subjects) describes a SVR rate of 35 percent, 26 percent for genotype 1 and 70 percent for others. This higher response rate in children could be related to factors such as earlier stage of disease, higher relative interferon dosage, or lack of co-morbid conditions or aggravating cofactors. Alternatively, this finding could simply be a statistical artifact of the small, uncontrolled trials. In any case, given the superiority of combination therapy with interferon and ribavirin in adults, it is unlikely that a large, randomized, controlled trial of interferon monotherapy will be undertaken in children with chronic HCV infection.

There are few data regarding the use of combination therapy in children. A recent abstract described a cohort of 61 children treated with 3 MU/m^2 of interferon thrice weekly, and 8, 12, or 15 mg/kg of ribavirin daily. The pharmacokinetic properties of the drugs were similar to those in adults, and the therapy was well tolerated, with dose-dependent anemia from the ribavirin that was somewhat less severe than that observed in adults. The 15 mg/kg ribavirin dose was chosen for a larger efficacy study which has recently been completed; results are expected in the coming months. There are no data regarding the use of the pegylated interferons in children.

Prevention of new HCV infections in older children requires education about high-risk behaviors. Although commercial body piercing and tattooing are not clearly associated with risk, self-tattooing and self-piercing with shared needles are fairly common practices and might be associated with HCV acquisition. Transmission of infection in intravenous drug users is well understood, but the risk from sharing straws or other implements for intranasal cocaine administration may not be appreciated by teenagers.

The primary target for prevention strategies should be perinatal transmission. Currently, universal testing of pregnant women for HCV infection is not recommended. Post-exposure immune globulin is not effective. Maternal HIV co-infection has been addressed with aggressive antiretroviral therapy. There are no safe measures to decrease maternal HCV viremia at delivery,

since interferon and ribavirin are contraindicated during pregnancy. If the importance of obstetrical factors is confirmed, changes may become necessary in the care of infected women.

In summary, HCV infection in children is not rare and is under-recognized. The natural history is either more benign or more prolonged when compared to adult-onset infection. Children may have a better response rate to current therapies, but well-designed studies have not yet been done. Prevention efforts should focus on perinatal transmission.

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Patients With Normal ALT Levels

Bruce R. Bacon, M.D.

At the 1997 NIH Consensus Development Conference on Management of Hepatitis C, it was concluded that "….treatment of patients with persistently normal ALT is not beneficial and may actually induce liver enzyme abnormalities."[1] Since that time, this issue has been controversial with some investigators supportive of treatment and others suggesting that no work-up or therapy is necessary for these patients. Approximately 30 percent of patients with chronic hepatitis C have normal ALT levels, and another 40 percent have ALT levels that are less than two times the upper limit of normal.[2] Most patients with normal ALT levels have mild degrees of inflammation with mild or no fibrosis and their rate of disease progression is reduced compared to those with elevated ALT levels.[3,4] However, some patients with persistently normal ALT levels can progress to advanced fibrosis and cirrhosis.[3–6]

The issue regarding treatment of these patients has often focused on how to proceed in patients with mild disease, recognizing that ALT levels may actually be just a proxy for mild histology. The best treatment trials that have been performed are the registration trials for FDA approval, and those have all required that patients have elevated ALT levels to be included in the study. Therefore, there are no large treatment trials of normal ALT patients. When interferon monotherapy was used for HCV patients with normal ALT levels, sustained response (SR) rates generally ranged from 15 percent to 20 percent. These SR rates are similar to the results of studies obtained when interferon monotherapy was used to treat patients with elevated ALT levels.

Since the NIH Consensus Conference recommendations were issued in 1997, treatment of chronic hepatitis C has progressed from interferon monotherapy to combination therapy using interferon and ribavirin, and more recently to pegylated interferon and ribavirin. A few studies of interferon plus ribavirin in chronic hepatitis C patients with normal or near normal ALT levels have been reported. Gordon and colleagues studied patients from one of the large registration trials in which a total of 1,744 patients with hepatitis C received either interferon and placebo or interferon and ribavirin for 24 or 48 weeks.[7] Of these, 105 individuals (6 percent) had minimally elevated ALT levels, defined as ≤ 1.3 times the upper limit of normal (ULN), at their entry visit. Histologic activity index and fibrosis scores were lower amongst these patients with baseline ALT levels ≤ 1.3 times the ULN. There was no difference in SR between patients with ALT levels ≤ 1.3 times the ULN (24.8 percent) compared to those with ALT levels > 1.3 times the ULN (26.8 percent) for all treatment groups. Lee and Sherman studied 19 patients with ALT levels that were either normal or < 1.5 times the ULN.[8] Nine of the 19 patients (47 percent) had an SR. In studies from our group at Saint Louis University, Di Bisceglie, et al. reported on a group of interferon monotherapy nonresponders who were re-treated with the combination of interferon and ribavirin.[9] In total, of 124 patients were studied; 24 had normal ALT levels and 100 had elevated ALT levels. There was no difference in SR between the two groups (26 percent vs. 34 percent). Further, we have coordinated an investigator-initiated multicenter study evaluating the use of interferon and ribavirin in treatment of naïve patients with chronic hepatitis C who have persistently normal ALT levels. One hundred seventeen patients have been enrolled

in this study and are currently in treatment or followup phases of the study. Thus, all reported studies have shown that SR rates for normal or near normal ALT patients are equivalent to those of elevated ALT patients when the combination of interferon and ribavirin is used.

Currently, the standard of care for most patients with chronic hepatitis C is to use the combination of pegylated interferon and ribavirin. Overall SR rates of about 55 percent can be achieved. There are no studies of normal ALT patients being treated with pegylated interferon and ribavirin, although a large investigator-initiated multicenter study is currently under way. When evaluating the effect of pegylated interferon and ribavirin, Manns and colleagues compared patients with minimal or no fibrosis to those with bridging fibrosis or cirrhosis.[10] When pegylated interferon and ribavirin were used as therapy, the SR rates for those with mild histologic changes were better (57 percent) than those with more advanced histology (44 percent).

In summary, approximately 30 percent of patients with chronic hepatitis C have normal ALT levels and another 40 percent have ALT levels < 2 times the ULN. The majority of these patients have disease that is histologically mild, but these patients can have progressive liver disease with the development of advanced fibrosis and cirrhosis. It no longer seems reasonable to conclude that SR rates for patients with normal ALT levels are any different than those for patients with elevated ALT levels. The issue at hand is whether or not patients with mild liver disease should be treated. There are numerous other factors which impact on this decision, including genotype, histology, patient motivation, symptoms, co-morbid illness, and the age of the patient. ALT levels may have less importance in deciding who should be treated.

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Patients With Advanced Disease

Teresa L. Wright, M.D.

The majority of patients with HCV infection have mild liver disease, and concern about this virus would be vastly reduced if it were not for the minority that progress to cirrhosis. All of the potentially life-threatening complications of HCV infection such as hepatocellular carcinoma, bleeding esophageal varices, life-threatening infections, hepatic synthetic failure, and intractable ascites occur in patients with advanced liver disease. Unfortunately, it is not possible to reliably identify those patients who are risk for developing cirrhosis. The management of HCV disease is further complicated because, in general, therapeutic interventions are more successful in patients with early disease than in those with advanced liver disease.

With that background, how successful are existing interventions in patients with advanced liver disease? First and foremost, available therapies are currently limited. Many patients with advanced HCV disease are not candidates for interferon plus ribavirin. Contraindications in this population include cytopenias (platelet counts less than 75 k/mm^3 and white cell counts less than 1,500/mm^3) and/or co-morbid conditions such as uncontrolled psychiatric disease that preclude therapy.

Data on safety and efficacy of interferon (standard or pegylated) with or without ribavirin in patients with compensated cirrhosis or transition to cirrhosis have often been derived from subgroup analysis of larger trials,[1–3] although in some studies, this population has been the sole focus of the trial.[4] In patients with sufficient platelets and white blood cells to tolerate therapy, pegylated interferon alfa 2b in combination with ribavirin has been studied at two different dosing regimens and compared to standard interferon plus ribavirin (Table 1). Viral clearance in patients with advanced liver disease was the similar with all three regimens (41–44 percent), but was lower in patients with advanced liver disease than in patients with minimal or no fibrosis (Table 1). Similar analyses have been performed in patients receiving combination therapy, which includes pegylated interferon alfa 2a (Table 2). In patients with advanced liver disease, viral clearance ranged from 43 percent in patients receiving pegylated interferon alfa 2a in combination with ribavirin to 21 percent in patients receiving pegylated interferon alfa 2a as monotherapy. Response was 33 percent in patients receiving standard interferon alfa 2b plus ribavirin (Table 2). As for the results from other studies,[2] sustained virological response with all three regimens was lower in patients with advanced liver disease than in patients without cirrhosis (Table 2). Comparisons between trials should not be performed without information about distribution of other variables, such as infecting genotype, that could influence response in the different treatment arms.

In patients with advanced liver disease receiving pegylated interferon alfa 2a in combination with ribavirin, the optimal dose of ribavirin appears to be 1,000 mg/1,200 mg, rather than 800 mg, and the optimal duration of treatment appears to be 48 rather than 24 weeks.[5] Efficacy of different doses of ribavirin in combination with pegylated interferon alfa 2b is under study. Median reductions in white blood cell count and platelet count are greater in patients receiving pegylated interferon than in those receiving standard interferon.[2–4] Thus patients with significant cytopenias in the setting of advanced liver disease who receive antiviral therapy should be monitored closely.

Table 1. Comparison of Treatment With Standard Interferon Alfa 2b Plus Ribavirin vs. Pegylated Interferon Alfa 2b in Combination With Ribavirin for 48 Weeks (Manns et al., Reference 2)

	IFN Alfa 2b (3mU tiw, 48 weeks) Plus Ribavirin 1,000 mg/1,200 mg	PEG IFN Alfa 2b (1.5 µg/kg SQ q week) Plus Ribavirin 800 mg/d	PEG IFN Alfa 2b (1.5/0.5 µg/kg SQ q week) Plus Ribavirin 1,000 mg/1,200 mg
SVR in patients with cirrhosis or transition to cirrhosis	41 percent (54/132)	44 percent (60/136)	43 percent (63/146)
SVR in patients no or minimal fibrosis	49 percent (164/336)	57 percent (189/333)	51 percent (175/345)

Table 2. Comparison of Treatment With Standard Interferon Alfa 2b vs. Pegylated Interferon Alfa 2a in Combination With Placebo or With Ribavirin (1,000–1,200mg/D) for 48 Weeks (Roche Data on File)

	IFN Alfa 2b (3mU tiw, 48 weeks) Plus Ribavirin 1,000 mg/1,200 mg	PEG IFN Alfa 2a (180 µg SQ q week) Plus Placebo	PEG IFN Alfa 2a (180 µg SQ q week) Plus Ribavirin 1,000 mg/1,200 mg
SVR in patients with cirrhosis or transition to cirrhosis	33 percent (N=54)	21 percent (N=34)	43 percent (N=56)
SVR in patients without cirrhosis	47 percent (N=390)	31 percent (N=190)	58 percent (N=397)

Another end point of therapy that is pertinent to patients with advanced liver disease is delay in histological disease progression. The premise is that therapy, while not clearing virus, achieves a "clinically meaningful end point" usually defined as a reduction by two or more points in the histological activity index. The clinical relevance of achieving such an end point is currently under evaluation in an NIH-sponsored study (the HALT-C trial) of suppressive therapy with pegylated interferon alfa 2a in preventing the development of complications of advanced liver disease in patients who have previously failed pegylated interferon plus ribavirin. Prior to the availability of results from this trial, it will be necessary to rely on analysis of subsets of patients with advanced liver disease included in multicenter trials of ribavirin plus pegylated interferon alfa 2a or alfa 2b combination therapy. Improvement in liver histology (defined as a reduction of two or more points in the histological activity index) is observed in 68 percent of

patients receiving pegylated interferon alfa 2b (1.5 μg/kg SQ q week) plus ribavirin 800mg qd for 48 weeks, compared with 69 percent of patients receiving standard interferon alfa 2b plus ribavirin.[2] Improvement in fibrosis score was seen less frequently (21 and 20 percent, respectively).[2]

During the lead-in phase of the HALT-C trial, on-treatment virological response has been observed in 30 percent of patients receiving pegylated interferon alfa 2a plus ribavirin who had previously failed standard interferon plus ribavirin.[6] Thirty-nine percent of patients required dose reduction of either interferon or ribavirin, but only 6 percent could not tolerate treatment.[6] Thus, pegylated interferon plus ribavirin, appears to be tolerated in the majority of patients with advanced HCV cirrhosis who have not yet developed clinical complications of their liver disease. Thus, it is likely that hepatitis C therapy can slow histological disease progression in patients with histologically advanced liver disease, and that sustained viral clearance can be achieved in a proportion of patients. Whether this "histological slowing" translates into reduction in development of life-threatening complications remains to be determined.

A more problematic group of patients are those with decompensated cirrhosis. Patients with HCV-related cirrhosis who meet criteria for listing for liver transplantation have a five year survival rate of only 50 percent.[7] There are small case series of treating patients awaiting liver transplantation[8,9] that suggest that viral clearance is achievable in a proportion of patients with advanced liver disease although adverse events, including potentially life-threatening adverse events, have been observed. If viral clearance is achieved, these patients may be virus-free after liver transplantation.[8]

Until complete data are available on the safety and efficacy of pegylated interferon plus ribavirin in patients with advanced decompensated HCV-disease, such patients should, when possible, be enrolled in clinical trials. Pegylated interferon plus ribavirin is clearly indicated in patients with compensated HCV disease who have pre-treatment platelet and white blood cell counts that are sufficient to accommodate the cytopenias associated with therapy, but treatment is relatively contraindicated in patients with decompensated cirrhosis, particularly in patients with Childs-Pugh-Turcotte scores of greater than 10.[6]

What of interventions in patients with HCV disease following liver transplantation? Hepatitis C infection of the graft is the rule following liver transplantation, and disease progression is accelerated compared to immune competent patients with HCV disease.[10] Moreover, once histological cirrhosis of the allograft occurs, the risk of complications of liver disease is even higher than in the immune competent patients with cirrhosis.[11] Variables associated with post-transplantation disease progression include pre-transplantation antiviral therapy, HCV RNA level at the time of transplantation, and advanced age of the organ donor, as well as treatment of rejection in the post-transplantation period.[10]

There has been interest in "pre-emptive" antiviral therapy early in the post-transplantation period as well as treatment of established liver disease of the allograft. Responses to standard interferon plus ribavirin are generally lower following liver transplantation than in immune competent patients. Moreover, since many patients have renal insufficiency secondary to immunosuppressive agents, ribavirin is poorly tolerated, and if used, ribavirin dose should be reduced. Studies of pegylated interferon with or without ribavirin are under way.

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Therapy of Acute Hepatitis C

Alfredo Alberti, M.D.

Acute hepatitis C is uncommon and difficult to recognize and to diagnose. The main reasons are the following: a) the incidence of new infections with HCV has greatly decreased during the past decade in all civilized countries; b) acute hepatitis C is often mild and asymptomatic; c) there is no specific diagnostic test to identify acute infection with HCV and to distinguish it from reactivation phases that may occur in chronic infection. As a consequence, acute hepatitis C has been difficult to study and there is still limited information about its natural history and optimal management strategies. Early studies, which were conducted mainly in cases with acute post-transfusion NANB (Type C) hepatitis, indicated that this condition has an extremely high propensity to become chronic. On the basis of these observations, and of the data on the treatment of chronic hepatitis C with interferon, a number of studies have been conducted since the early 1990s to assess whether interferon therapy could prevent chronic outcome of acute hepatitis C.

Seventeen studies on the treatment of acute HCV infection with interferon have been published either as full papers (13) or as letters/abstracts (4), including 7 randomised controlled trials, 5 controlled but not randomised trials, and 5 studies without an untreated control group. Of these latter, 2 were randomised trials in which different treatment schedules were compared. In all these studies interferon (alfa or beta) monotherapy was used; there are no available reports on the treatment of acute hepatitis C with interferon plus ribavirin combination therapy or with the pegylated interferons. Overall, 295 treated patients and 162 untreated cases with acute hepatitis C have been included, with a sample size of 6–97 patients in each individual study. Analysis of the 17 published reports reveals great heterogeneity with respect to: (1) inclusion criteria and patients characteristics (for example, some studies included asymptomatic cases seen during prospective surveillance of transfused or otherwise exposed patients while others included only symptomatic cases identified clinically; 7 studies were conducted in PTH cases, 6 in patients with non-transfusion related hepatitis C, and 4 included a mixture of the two subgroups); (2) timing of treatment initiation (early or delayed treatment after infection or after clinical onset); (3) type of interferon used (interferon alfa: 12 studies, interferon beta: 5 studies); (4) dose and schedule of administration (total cumulative dose ranging from 8.4 MU to 780 MU, with daily administration in 4 studies, tiw administration in 10 studies, and daily induction followed by tiw administration in 3 studies); (5) duration of post-treatment followup (ranging from 6 to 36 months); (6) end points of biochemical (ALT) response only: 5 studies; biochemical (ALT) and virological (HCV-RNA) response: 12 studies.

Pooling all data from the 17 studies, an end-of-therapy biochemical (ETR-ALT) and virological (ETR-HCV-RNA) response was seen in 76 percent (range 15–100 percent) and in 82 percent (37–100 percent) of treated patients and in 24 percent (10–44 percent) and in 10 percent (0–20 percent) of untreated patients, respectively. A sustained biochemical (SR-ALT) and virological (SR-HCV-RNA) response was seen in 61 percent (25–100 percent) and 62 percent (37–100 percent) of treated patients and in 26 percent (16–50 percent) and 12 percent (0–20 percent) of untreated cases, respectively.

Results of RCTs

Among the 7 RCTs published, 4 were conducted in PTH cases with an identical schedule of 3 MU tiw of interferon alpha given for 12 weeks. These 4 studies were homogeneous and could be pooled together in a recent meta-analysis (Cochrane review). According to the results of this analysis, the ETR-HCV-RNA was 42 percent (95 percent CI 30–56 percent) with interferon vs. 4 percent (0–13 percent) with no treatment ($p<0.00001$), while SR-HCV-RNA was 32 percent (21–46 percent) with IFN vs. 4 percent (0–13 percent) without therapy ($p= 0.00007$). IFN therapy was associated with 45 percent (31–59 percent, $p=0.00001$) and 29 percent (14–44 percent, $p=0.0002$) increase in ETR-HCV-RNA and SR-HCV-RNA, respectively, compared with no treatment.

These results prove that interferon therapy is associated with a significant reduction of chronicity when given to patients with post-transfusion acute hepatitis C, even using a relatively low dose for a relatively short period. However, around 2/3 of the patients treated with this regimen still developed chronic infection.

Other Studies

Other studies have used more aggressive treatment schedules with higher IFN dosages and longer periods of administration, and these approaches have usually resulted in higher rates of sustained virological response. Unfortunately, most of these studies were conducted without a randomised untreated control group. Furthermore, many of them included patients with acute symptomatic hepatitis C often acquired through a non-transfusion source. In these cases, rates of spontaneous resolution of acute hepatitis C might be significantly higher than in asymptomatic cases with PTH. In studies where 5–10 MU of interferon were given daily for 4–12 weeks or up to ALT normalization, followed by the same or a lower IFN dose given tiw for 20–40 additional weeks, rates of sustained virological response reached 83 to nearly 100 percent. In other studies, conducted in similar patient cohorts treated with lower doses of IFN (3–6 MU tiw for 3–6 months), rates of sustained virological response were between 37 and 64 percent. In one study comparing different regimes of daily beta IFN, there was a clear dose dependent effect on sustained response rates. In those studies where an untreated control (although not randomised) group was included for comparison, rates of spontaneous resolution were usually lower (8–21 percent) although a statistically significant difference was rarely obtained due to the small number of patients included. These results indicate that high rates of sustained virological response (24 week SR) can be achieved in acute hepatitis C with IFN monotherapy, in a setting where the expected rate of spontaneous resolution can be estimated around 10–40 percent.

Predictors of Response

Pre-treatment HCV-RNA levels were reported in 5 studies. In 3 of them there was a statistically significant correlation with sustained virological response that was higher with lower viraemia. Interestingly, this association was lost when high dose IFN (5–10 MU daily) schedules were used. The HCV genotype was reported in 7 studies, but in only 2 of them was there a significant association between the HCV type and response (better with HCV2/3 and worse with HCV1).

Tolerability Profile

Detailed description of side/adverse effects seen during therapy has been reported only in 7 studies, with a total of 145 treated patients. The tolerability profile of IFN therapy was very similar to that usually observed when treating patients with chronic hepatitis C. Therapy was well tolerated also in patients with jaundice or very high ALT levels. No ALT flares or deterioration of liver function were observed during therapy, apart from one single patient treated with 10MU daily who developed "acute lobular hepatitis" after HCV-RNA clearance and required a short period of steroid treatment. Overall, the available data do not indicate higher rates of IFN associated side/adverse effects or unexpected adverse effects in patients with acute hepatitis C when compared with what is reported in patients treated for chronic hepatitis C.

Unsolved Issues and Conclusions

Whom to treat: Acute HCV infection may be seen in individuals with minimally elevated or completely normal ALT and serum HCV-RNA positivity following known exposure or needle-stick injury or in sick patients with symptomatic acute hepatitis C, exemplified by very high ALT levels and jaundice. Available data would indicate that the effect of IFN therapy is independent of the clinical phenotype, although more data is needed to better define outcomes with and without therapy in different patient subgroups and to determine safety of therapy in severely ill cases.

***When to start therapy*:** Immediate treatment of all cases with acute HCV infection means giving unnecessary therapy to those who would have recovered spontaneously. A strategy of delaying therapy by 2–3 months after diagnosis should allow giving treatment only to patients with a high risk of chronic outcome. This approach might be particularly rational in those subgroups of patients in which a high rate of spontaneous recovery is expected, such as children, young adults (particularly women), and patients with jaundice. It remains to be defined whether delaying therapy could reduce its efficacy due to HCV quasispecies expansion towards a more heterogeneous and resistant virus population, as the infection evolves into chronicity. Available data, albeit limited, tends to suggest that delaying therapy by 2–3 months does not compromise the probability of a favorable response to interferon.

How to treat: The optimal schedule in terms of risk/benefit and cost/effectiveness ratio is far from having been defined. Available data would indicate that the minimum requirement for obtaining a significant benefit compared to untreated patients is to use 3 MU tiw for at least 12 weeks. With such a regimen, however, only between 30 and 40 percent of treated patients develop a sustained virological response. More aggressive regimens, based on induction with daily IFN (5 to 10 MU) followed by tiw therapy for 4–6 months, may allow the achievement of a sustained virological response (24 week SVR) in almost 100 percent of the cases. On the basis of these findings, studies with the PEG-IFNs are urgently needed. Combination therapy with addition of ribavirin might not be essential to treat most cases of acute hepatitis C, but this also needs to be explored in clinical trials.

Long-term benefit of treatment: More prolonged followup of patients with acute hepatitis C treated with interferon is needed. Most published studies refer to sustained virological response at 24 weeks after therapy. Studies on the natural history of acute hepatitis C have indicated the need for an accurate and prolonged virological followup to predict long-term outcomes as transient phases of HCV-RNA negativity occur after acute phase in patients with chronic evolution of hepatitis C. Furthermore, long-term clinical outcomes should be accurately modeled in treated and untreated patients considering the low rate of clinically relevant chronic sequelae seen during the first two decades of infection with HCV. Nevertheless, if a near 100 percent eradication of HCV can be achieved with IFN therapy in acute infection, it seems quite difficult not to believe that this result should transfer into significant clinical benefit in many of the patients.

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Hepatitis C and HIV

David L. Thomas, M.D.

An estimated 150–300 thousand persons are infected with both hepatitis C virus (HCV) and HIV in the United States. Although the management of hepatitis C in HIV infected persons in 2002 is largely predicated on data from persons without HIV, it is important to appreciate the extent to which HIV infection may modify the transmission, natural history, diagnosis, and treatment of hepatitis C.[1]

Transmission

In more than 60 percent of published studies, the rate of HCV transmission from an HIV/HCV co-infected mother to her infant is greater than from HIV uninfected mothers. Increased heterosexual HCV transmission from HIV/HCV co-infected persons also has been reported, but in fewer than half of studies. Nonetheless, these data do not substantially modify existing United States Public Health Service recommendations for recognition and prevention of HIV and HCV transmission.[2,3]

Natural History

In the majority of published studies, progression of hepatitis C to cirrhosis and end-stage liver disease occurs more rapidly and in a greater proportion of HIV/HCV co-infected persons, and in several hemophilia cohorts and HIV treatment clinics, end-stage liver disease is *a* or *the* leading cause of death among HIV infected persons. Although the risk of cirrhosis associated with HIV infection varies substantially in different settings, in a meta-analysis, Graham and coworkers estimated that the average risk of progressive liver disease is 2.9-fold (95 percent CI, 1.7–5.0) higher in HIV/HCV co-infected persons.[4] Large prospective studies are needed in unbiased HIV/HCV co-infected populations to characterize the risk of cirrhosis more precisely. In the meantime, decisions regarding the timing of medical treatment and the frequency of monitoring HIV/HCV co-infected persons (e.g., by liver biopsy or with fibrosis markers, if available) should be commensurate with the observed increased risk and rate of progression to end-stage liver disease.

Diagnosis and Screening

Because the prevalence of hepatitis C is increased in HIV infected persons and HIV/HCV co-infected persons have an increased risk of cirrhosis and HAART-related liver toxicity, the United States Public Health Service and Infectious Diseases Society of America recommend that all HIV infected persons be screened for hepatitis C by using an enzyme immunoassay for detection of antibodies to HCV.[3] HCV antibodies can be detected in the majority of HIV/HCV co-infected persons. However, in some studies HCV antibodies were not be detected in up to 10 percent of HIV/HCV co-infected persons, especially in those with advanced HIV-related immune suppression (CD4+ lymphocytes < 100/mm^3). Thus, it is reasonable to test for HCV

RNA in HCV antibody negative, HIV infected persons with unexplained liver enzyme elevations.

Treatment

No medications are approved by the United States Food and Drug Administration for the treatment of HCV infection in HIV infected persons, reflecting the absence of completed, randomized controlled trials investigating the treatment of more than 100 HIV/HCV co-infected persons. Therefore, the timing and choice of medical treatment for HIV/HCV co-infected persons are largely driven by their increased rate of progression of liver disease and the results of treatment of HIV uninfected persons.

Nonetheless, a number of important issues in the treatment of hepatitis C in HIV infected persons can be addressed by accumulating published and formally presented data.

1. Sustained virologic responses can be achieved in HIV infected persons. Soriano et al. have demonstrated loss of HCV RNA from serum for >3 years after a course of interferon alpha in HIV infected persons.[5]

2. The addition of ribavirin to interferon alpha improves the likelihood of on-treatment (and presumably sustained) virologic responses in HIV/HCV co-infected persons. In an interim analysis of data from 110 HIV/HCV co-infected persons randomized to interferon alfa-2b with ribavirin or placebo, HCV RNA was undetectable after 12 weeks of therapy among 23 percent of persons receiving combination therapy compared to 5 percent of those receiving interferon alone.[6]

3. On-treatment virologic responses to pegylated interferon and ribavirin are better than responses to unpegylated interferon alpha and ribavirin. In ACTG a5071, in which 134 persons were randomized to pegylated interferon alpha plus ribavirin or unpegylated interferon alpha plus ribavirin, week 24 virologic responses were noted in 15 percent of those in the unpegylated arm vs. 44 percent of those randomized to pegylated interferon alpha, an effect that was also observed among persons with genotype 1 infection (7 percent vs. 33 percent, respectively).[7]

4. Although in vitro studies suggest ribavirin may diminish the efficacy of AZT, d4T, and 3TC, and increase levels of ddI, in several small published and presented case series, HIV RNA levels do not increase more in HIV/HCV co-infected persons taking ribavirin than in controls. Given apparent benefits and the burden of disease, many experts currently recommend its use in the treatment of hepatitis C in HIV/HCV co-infected persons, with careful monitoring.

5. As with HIV uninfected persons, the likelihood of a sustained virologic response in HIV/HCV co-infected persons varies by HCV genotype, pretreatment immune status, and other factors like HCV RNA level, stage of liver disease, gender, possibly race, and duration of treatment, which may need to be longer when virologic responses are delayed and in immunosuppressed persons.

6. Some HIV/HCV co-infected persons will not be able to take existing medical therapies, and liver transplant is rarely available for HIV/HCV co-infected persons.

Conclusion

Given the mounting morbidity and mortality associated with hepatitis C in HIV infected persons, the management tools (e.g., HCV RNA testing and liver biopsy) and therapies (e.g., pegylated interferon alpha and ribavirin) recommended for management of hepatitis C in persons without HIV should be made available for HIV/HCV co-infected persons while research is vigorously conducted to demonstrate their optimal use.

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Injection Drug Use and Hepatitis C

Brian R. Edlin, M.D.

Injection drug users (IDUs) constitute the largest group of persons infected with the hepatitis C virus (HCV) in the United States, and most new infections occur in IDUs. Controlling the HCV epidemic, therefore, will require developing, testing, and implementing prevention and treatment strategies that will be effective in persons who inject drugs. Preventing morbidity and mortality from HCV will require reducing exposure to HCV, reducing infection among those exposed, and reducing disease among those infected. Injection drug use could be greatly reduced if all those who needed substance abuse treatment could get it (prevention of exposure). HCV spread among drug users can be prevented if drug users have access to sterile syringes, HCV counseling and testing, and outreach programs that teach them how they can avoid acquiring and transmitting the virus (prevention of infection). Finally, barriers to medical treatment must be overcome so that drug users can benefit from advances in HCV treatment (prevention of disease).[1] HCV treatment may also reduce transmission (prevention of infection), because HCV-infected IDUs are the source for most HCV transmission in the United States. Efforts are particularly important to identify persons with new HCV infections, in whom treatment may be more effective during the acute phase than later, and those with advanced hepatic fibrosis, in whom treatment may improve survival.

Caring for drug users presents special challenges to the health care team that require patience, experience, and tolerance. Fortunately, substantial research and clinical experience in the prevention and management of chronic viral infections among IDUs, especially HIV infection, has led to the development of effective principles for engaging drug users in health care relationships (Table).[2–5] Learning from this experience will be critical for efforts to control HCV. Successful programs invariably adopt a respectful approach to substance users, understand the medical and behavioral sequelae of addiction, and refrain from moralistic judgments. These strategies reflect a harm reduction approach.[6,7] Harm reduction strategies help patients reduce high-risk behaviors without imposing unrealistic demands for global change. When ceasing all drug use is not likely in the immediate future, other measures must be taken to help patients reduce the harmful consequences of injection drug use.[8,9]

Decisions about the treatment of HCV infection in patients who use illicit drugs, as in other patients, should be made by the patients together with their physicians based on individualized risk-benefit assessments.[1] Adherence, psychological side effects, and the possibility of reinfection present challenges to effective treatment for some drug users. Fortunately, an array of effective strategies exists to overcome each of these challenges. Attention to ensuring optimal adherence is important for all patients, not just those who use drugs.[10] This is so because although certain risk factors for noncompliance have been identified, including depression, psychological stress, homelessness, lack of social support, and drug use, physicians are not able to predict accurately which patients will adhere to a treatment regimen.[11] Effective strategies for improving adherence range from basic clinical practices—such as establishing a consistent, trusting physician-patient relationship, providing clear information

Table. Principles for managing health care relationships with substance-using patients.

1. Establish a climate of mutual respect.
2. Maintain a professional approach that reflects the aim of enhancing patients' well-being; avoid creating an atmosphere of blame or judgment.
3. Educate patients about their medical status, proposed treatments, and their side effects.
4. Include patients in decision-making.
5. If possible, establish a multidisciplinary team consisting of primary care physicians, HIV specialists, psychiatrists, social workers, and nurses.
6. Have a single primary care provider coordinate the care delivered by such a team to maximize consistency and continuity.
7. Define and agree on the roles and responsibilities of both the health care team and the patient.
8. Set appropriate limits and respond consistently to behavior that violates those limits.
9. Minimize barriers to participation (penalties for missed visits, etc.).
10. Recognizing that patients must set their own goals for behavior change, work with patients to achieve commitment to realistic goals for healthier behaviors.
11. Acknowledge that abstinence is not always a realistic goal; emphasize risk reduction measures for patients who continue to use drugs.
12. Acknowledge that sustaining abstinence is difficult and that success may require several attempts.
13. Be familiar with local resources for the treatment of drug users.

about intended effects and side effects of medication, and paying careful attention to perceived side effects—to specialized tools such as electronic reminder systems, directly observed therapy, and cash incentives.[12–17] Simplifying complex treatment regimens, treating depression, or helping a homeless patient find housing can help improve adherence. Patients may also benefit from counseling addressing individual barriers to and facilitators of adherence in the patient's life.

The psychological side effects of interferon-based regimens for the treatment of HCV infection are of concern in all patients. Interferon may have severe psychological side effects in patients with or without pre-existing psychiatric disorders.[18,19] To minimize psychological toxicity, all patients should be screened for depression and other mental health conditions before undergoing HCV treatment, treated for these conditions if necessary, and monitored for them during HCV treatment.

Because those successfully completing HCV therapy may be at risk for reinfection, drug users need detailed counseling and support to avoid risky injection practices in case they continue or return to injecting drugs. Those who inject drugs after receiving effective treatment for HCV infection can avoid reinfection by using a new sterile syringe for each injection and by not sharing their injection equipment with other users.[20,21] There are 174 syringe exchange programs in 120 cities in 34 states in the United States, and the number is increasing yearly. For drug users without access to such programs, physicians in at least 46 states are allowed by law to prescribe syringes so that their patients can avoid acquiring and transmitting bloodborne infections.[22–24] IDUs can master safe injection practices, and many do inject safely. When given access to sterile syringes, IDUs readily make use of them, reducing their high-risk behavior[25–27] and rates of disease transmission.[28,29] Physicians should refer patients who inject drugs to syringe exchange programs or, if necessary, prescribe syringes for them. HCV may be more readily transmitted than the human immunodeficiency virus (HIV) through the sharing of injection equipment other than syringes, such as "cookers" (bottle caps, spoons, and other containers used to dissolve drugs) and "cottons" (filters used to draw up the drug solution into a syringe).[30] Thus, it is particularly important for physicians to instruct their patients not to share these items.[20,21]

All injection drug users should be offered treatment for substance abuse and such treatment should be provided to those wishing it. Medical services should be integrated with substance abuse treatment.[3] Alcohol treatment is particularly important because of the strong effect of heavy alcohol intake on the progression of hepatitis C. Finally, all patients with HCV infection should be instructed in how to avoid transmitting the infection to others. Patients should be warned that their blood may be infectious even in minute quantities. Those who inject drugs should be instructed not to share syringes or any other injection equipment with other persons and to avoid blood contact with others. They should be given biohazard sharps containers or instructed to safely dispose of injection equipment in puncture-resistant containers.[31]

Clinical Data

There is abundant evidence that when treatment strategies for drug users take into account the circumstances of their lives, very high rates of adherence can be achieved.[11,15–17,32–38] Several recent studies have demonstrated the safety and effectiveness of hepatitis C treatment in drug users, even when they are not completely abstinent from drug use.[39–41] Backmund et al. reported a 36 percent sustained virologic response rate in 50 injection drug users who were treated simultaneously for HCV infection and substance abuse, even though 80 percent of the patients relapsed to drug use.[39] Sustained response rates were not significantly different for patients who relapsed and those who did not. All patients were treated and supervised by physicians who specialized in both hepatology and addiction medicine. Patients who relapsed to drug use were offered opiate replacement therapy and were allowed to continue their HCV treatment even if they injected heroin again. The strongest predictor of virologic response was whether patients continued to keep their appointments; 45 percent of those who kept $\geq$ 67 percent of their appointments but only 6 percent of those who did not had sustained virologic responses. This study demonstrates the importance of combining expertise in both hepatology and substance

abuse and maintaining strong relationships with patients that can be sustained even through relapse to drug use.

Sylvestre et al. have treated 67 methadone maintenance patients with combination interferon/ribavirin, with an interim sustained virologic response rate in the first 59 patients of 29 percent, a rate identical to that in a comparison group of nonopioid-dependent patients.[40] No serious side effects occurred, although 61 percent of the patients had a prior psychiatric diagnosis. Response rates were not significantly different in patients who did or did not have 6 months of sobriety, nor in patients who did or did not consume alcohol. They were not significantly worse in patients who continued using drugs unless they used every day. This study demonstrates that HCV can be effectively treated in patients receiving maintenance opiate replacement therapy despite substantial pre-existing psychiatric disease and despite ongoing, intermittent drug use.

Finally, Backmund et al. reported no reinfection during 24 weeks in 10 patients who continued to inject heroin.[39] They carefully instructed their patients how to avoid acquiring HCV when injecting drugs. Dalgard et al. reported one reinfection during 5 years in 9 patients who relapsed to injection drug use after sustained virologic responses to HCV treatment.[41]

Success in treating HCV infection in IDUs will require collaboration between experts in hepatitis and substance use to create programs specifically designed for drug users. Efforts to control HCV, including both prevention and treatment, can benefit from the expertise of those with experience working with drug users. Substance abuse treatment professionals have expertise working with drug users in treatment. Harm reduction workers and many substance abuse researchers have expertise working with out-of-treatment drug users. And many AIDS medical providers have expertise providing medical care to drug users both in and out of substance abuse treatment. Involvement of these professionals in HCV prevention and treatment efforts will greatly improve their effectiveness.

A sound policy for the control of the hepatitis C epidemic will require implementing prevention and treatment programs designed for IDUs, the group most severely affected by the epidemic.[42] Controlling the HCV epidemic, therefore, will require further research to develop and test prevention and treatment strategies that will be effective in persons who inject drugs. In the meantime, however, substantial progress can be made to control hepatitis C if existing knowledge and resources are brought to bear.

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Alcohol and Hepatitis C

Marion G. Peters, M.D., M.B.B.S., and Norah Terrault, M.D.

Excess alcohol consumption can worsen the course and outcome of chronic hepatitis C.[1–3] However, adverse effects of moderate amounts of alcohol intake have not been clearly shown.[4] Alcohol use has been reported in some studies to be associated with higher HCV RNA levels and lower responses to therapy.[5] Despite a large number of publications on the topic of alcohol and hepatitis C, current evidence from the literature is not adequate to provide clear and definitive recommendations regarding alcohol use in patients with hepatitis C. In the absence of conclusive data, a conservative approach is taken and abstinence is usually recommended.

What Level of Alcohol Intake Is Harmful in Chronic Hepatitis C?

Poynard and coworkers compared liver histology of patients with hepatitis C drinking >50 g per day to that of non-drinkers and found a 34 percent increased rate of progression of fibrosis in heavy drinkers.[1] Associations between fibrosis progression and lesser amounts of alcohol intake were not significant, but the measurement of alcohol intake was assessed in a uniform, standardized manner. The HCV National Register Steering Group in the UK traced 924 patients who had received an anti-HCV-positive unit of blood for an average of >10 years after transfusion and assessed alcohol intake using validated questionnaires.[6] Liver-related deaths were increased among those who drank >20 units per week (approximately 30 g per day) in both patients with hepatitis C and controls. The Dionysos study analyzed hepatitis virus markers, alcohol intake (assessed by questionnaires of daily and lifetime intake), and clinical and biochemical evidence for liver disease among 6,917 unselected residents of two Northern Italian cities.[3,7] In all, 2.3 percent had HCV RNA and 62 percent drank alcohol, including 21 percent who drank more than 30 g per day. Both control subjects and persons with HCV who drank more than 30 g per day for >10 years had a threefold higher risk of cirrhosis (95 percent CI = 1.2 to 7.4, $p<0.01$). Intake below 30 g per day did not increase the risk of clinically apparent cirrhosis, but histology was not assessed in most patients. Harris and coworkers analyzed factors associated with cirrhosis among 206 patients who developed hepatitis C after transfusion and were followed for an average of 15 years in addition to a cohort of controls who were transfused but did not develop hepatitis C.[8] Among those with hepatitis C, 17 percent developed cirrhosis. The risk of cirrhosis increased fourfold among those who were also heavy drinkers (>80 g per day). Corrao and Arico analyzed results from two hospital-based, case-control studies of 285 patients with cirrhosis and 417 controls.[4] A lifetime daily alcohol intake of >50 g per day was associated with an increased risk of cirrhosis in both HCV-positive and negative subjects. The combination had an additive effect on the risk, and these risks were multiplied (synergism) at very high levels of alcohol intake (>125 g per day). Wiley and coworkers analyzed factors associated with more advanced liver disease in a cohort of 176 patients who underwent liver biopsy for chronic hepatitis C.[2] Alcohol intake of > 80 g daily was associated with a higher rate of cirrhosis (56 percent vs 22 percent) and an increase in the estimated rate of progression of fibrosis. In a study from Japan, Khan and Yatsuhashi found higher degrees of fibrosis on liver

biopsies from patients with chronic hepatitis C who drank alcohol compared to those who did not, and this increase was seen with both heavy (>80 g per day) and "moderate" (<80 g per day) alcohol intake.[9] Further delineation of effects of lower levels of alcohol intake were not given. Excess alcohol intake can also predispose to the development of liver cancer.[10] Thus, multiple studies have shown that heavy alcohol intake increases the risk of cirrhosis and liver cancer in hepatitis C, but the effects of moderate alcohol intake have not been adequately evaluated.

Are There Gender Differences in Effect of Alcohol on Progression of HCV Infection?

Chronic hepatitis C is often milder in women, but women may be more sensitive to the adverse effects of alcohol. The Dionysos cohort study found the risk of cirrhosis was twice as high in women as in men with the same alcohol intake.[3,7] Wiley et al. found a lower alcohol threshold for development of cirrhosis in women.[2] Thus, women may be at increased risk of alcohol effects on chronic hepatitis C.

What Are the Effects of Alcohol Consumption on Treatment of Hepatitis C?

Alcohol can affect the outcome of therapy in decreasing adherence or interfering with the antiviral actions of interferon or combination therapy. Virtually all large trials of therapy of hepatitis C have excluded persons who have a recent history of alcohol abuse, requiring a one- to two-year period of abstinence before therapy is initiated. However, the need for a period of abstinence has never been shown. Among patients treated for hepatitis C, a proportion continued drinking, and the ultimate response rate correlated inversely with the level of alcohol intake during therapy. The mechanism of the decreased response rate in patients drinking alcohol has not been defined. Some studies have shown that alcohol intake is associated with higher levels of HCV RNA[1,5] but other studies have not,[2,3,10] and the increase in HCV RNA levels with drinking alcohol has been modest. Thus, continued alcohol intake during therapy is likely to adversely affect the response to treatment, and both counseling and monitoring before and during therapy is recommended.

Does Alpha Interferon Therapy Cause Increase in Rate of Relapse Among Persons With a History of Alcohol Abuse or Dependence?

Relapse in alcohol intake during alpha interferon therapy has been reported, but the rate of relapse has not been compared in studies using untreated control patients. Nevertheless, the depression, irritability, and anxiety that occurs in 20–30 percent of patients treated with alpha interferon is likely to be difficult for the patient with a recent history of alcohol dependence and predisposition to relapse.

Conclusions

While the effects of heavy daily alcohol intake on the course of chronic hepatitis C appear to be incontrovertible, lesser amounts of alcohol may not be harmful. On the other hand, abstinence appears to be prudent for the patient with chronic hepatitis C, particularly while receiving a course of alpha interferon or combination therapy. Patients with a history of alcohol abuse or dependence should be asked to be abstinent for a period before starting therapy and need to be supported by professional counseling and monitoring during therapy. Better studies using validated instruments to measure alcohol intake in larger numbers of patients, followed for longer periods and with careful histological documentation, are needed to better define the effects of moderate alcohol intake on chronic hepatitis C and the need for abstinence before and during therapy. At the present time, there is no reason to withhold antiviral therapy of chronic hepatitis C from the patient with a history of alcoholism as long as adequate support can be provided during the period of therapy.

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Special Populations

Doris B. Strader, M.D.

The current recommendations for the ***management*** of patients with chronic hepatitis C are derived from a number of excellent multicenter trials. However, these trials primarily involve the ***treatment*** of a ***select group*** of patients with a single therapy, interferon plus ribavirin in combination. The selection of appropriate candidates for therapy involves an informal assessment of the patient's eligibility for treatment, followed by *screening* of all eligible candidates. It is unclear how many patients are not initially assessed as eligible, yet among those who are considered eligible and subsequently screened for therapy, reports from recent clinical trials indicate that 30–50 percent do not satisfy inclusion criteria.[1–4] The most common reasons for exclusion include severe psychiatric illness; active alcohol and substance abuse, comorbid illnesses such as autoimmune disease, hemophilia, and renal disease; decompensated liver disease; normal ALT; and refusal to participate. In addition, recent data on the response rate of those who receive treatment with combination therapy (standard or pegylated interferon plus ribavirin) suggest that at best, 50 percent achieve a sustained viral response (SVR).[5–7] These data indicate that at least 60 percent of anti-HCV-positive patients are either ineligible for therapy or do not respond to the available therapy. This suggests that the bulk of data obtained regarding hepatitis C and the management recommendations that followed were gathered from a small minority of pristine patients. While extrapolations regarding the management of the larger population of patients with HCV and confounding medical problems were made, the body of emerging data indicates that this may not have been appropriate. It is evident from previous discussions during this Conference that some exclusion criteria may have been too rigid, and that the reported response and adverse event rates may not be widely applicable. As a result, it appears that a large proportion of patients with HCV do not benefit from current antiviral therapy. What is missing from the literature is management guidance with respect to this large group of patients.

Before management decisions can be made, it is necessary to ask several important questions. First, **"Is current anti-HCV therapy optimal?"** Clearly, if therapy is optimal, all available resources should be channeled into treating as many patients as is safely possible. However, if available therapy is not optimal, research into alternative therapies should be pursued. Optimal therapy should be considered both safe and efficacious among the broadest cohort of affected patients. Current accessible data from anti-HCV treatment trials with pegylated interferon plus ribavirin report SVRs of approximately 50 percent among the relatively small group who qualify for treatment. This compares favorably with previously reported overall SVRs of 38 percent among those treated with standard interferon plus ribavirin. While few published data exist regarding the response rates of standard IFN plus ribavirin post-marketing, review of a few studies, as well as unpublished data obtained from several investigators indicates that the actual observed SVR is closer to 15–25 percent.[1,2] Although the SVRs with pegylated IFN plus ribavirin are expected to be higher, using the above data it is likely that less than 50 percent of treated patients will achieve an SVR. Therefore, it seems prudent to encourage research into novel forms of therapy.

Preliminary work on a number of potential candidates is already under way. It appears that as with therapy for HIV, therapy for HCV may require a multi-drug approach that exploits the replicative process at various stages, thereby containing, or at best eliminating, infection. Possible therapies include protease inhibitors, helicase inhibitors, NS5B RNA-dependent RNA polymerase blockers, modified ribavirins, and HCV immunotherapy.[8] These and other novel therapies will be discussed in detail in a subsequent discussion and may be the best hope for successful treatment of hepatitis C.

Second, **"In lieu of other therapies, what can be done to increase the eligibility of HCV-infected patients currently considered ineligible for treatment?"** A great deal of effort has recently been expended in attempts to enlarge the pool of eligible candidates, therapy either by liberalizing the inclusion criteria or by prophylaxing against or aggressively treating common side effects. Crude estimations from available data suggest that among those excluded from treatment trials, 20 percent have ongoing alcohol abuse, 19 percent have severe psychiatric illness, 12 percent use illicit intravenous drugs, 10 percent have comorbid disease, 10 percent have decompensated liver disease, 5 percent have normal ALT, and the remainder refuse therapy, are of advanced age, are undergoing evaluation for treatment, or are homeless. Treatment strategies for those with alcohol or drug abuse, normal ALT, co-infection with HIV, and those with organ transplants have been extensively discussed during the course of this Conference. While not discussed herein, there are some helpful data regarding the management of patients with HCV and hemophilia, renal disease, autoimmune hepatitis, severe psychiatric disease, and anemia. For example, recent studies in hemophiliac children with HCV suggest that therapy with IFN plus ribavirin is safe and well-tolerated in carefully monitored patients.[9] Conversely, data show that hepatitis C is common among hemodialysis patients and may adversely affect long-term graft survival in renal transplant recipients. Unfortunately, ribavirin is not dialyzed during standard dialysis and is associated with a dose-dependent hemolytic anemia, thereby limiting its use. Likewise, therapy of hepatitis C after renal transplantation has been disappointing. While one study showed an encouraging 16 percent sustained viral response rate and a 3 percent rejection rate, several others have shown a 50 percent incidence of graft rejection in renal transplant recipients.[10] As a result, an upcoming NIH workshop is planned to define the impact of HCV on the morbidity and mortality of those with end-stage renal disease as well as identify appropriate HCV treatment strategies in such patients. Trials in patients with HCV and autoimmune disease (hepatitis, sarcoidosis, SLE, etc.) advocate primary treatment of the autoimmunity as it appears that the risk of augmenting HCV with steroids is less than the risk of exacerbating autoimmune disease with interferon.[11] However, it is unclear whether this recommendation is absolute or whether there are "degrees" of autoimmunity (low ANA, mild disease) for which treatment with interferon is not contraindicated. Finally, attempts to increase the number of patients completing the full course of HCV antiviral therapy have been relatively successful using prophylactic antidepressants, aggressively treating interferon-induced depression, and advocating the use of erythropoetin or GMCSF for hematopoetic side effects.[12,13]

It is clear that the approach of liberalizing inclusion criteria and aggressively treating side effects may be laudable and reasonable among some patients, particularly those with genotypes 2 or 3 in whom the likelihood of achieving a SVR is approximately 80 percent. However, this approach may be more difficult to defend when considering those with less favorable genotypes and severe coronary or cerebrovascular disease, severe diabetes, mental retardation, seizures or

neurologic disorders, or cytopenias. In addition, there are groups of patients for whom the safety and efficacy of IFN plus ribavirin are less clear, specifically the elderly and African-Americans. It is reasonable to assume that patients with severe CAD or cerebrovascular disease are at increased risk for the potential adverse effects of hemolytic anemia. Similarly, interferon has been suggested to increase insulin resistance and it is possible that severe diabetes may complicate response to HCV antiviral therapy by its affects on hepatic steatosis. However, to my knowledge, no data exist regarding the treatment of HCV-infected patients with mental retardation, seizures or neurologic disorders, and the elderly. By contrast, a great deal of data is beginning to surface with respect to the disparity in response to antiviral therapy among patients of different racial groups. Although the numbers of patients are small, the data suggest that African-American patients with HCV are less likely to respond to IFN plus ribavirin than whites, Hispanics, or Asians. In addition, some trials indicate that African-American patients are more likely to suffer treatment side effects. At present, the NIH is conducting a trial evaluating the efficacy of IFN plus ribavirin therapy among African-American patients infected with HCV.

In this author's view, the potential risk of adverse events does not appear to be balanced by the small potential benefit of a sustained viral response in the patient groups described above. Even if the goal is halting the progression of fibrosis, an appropriately designed prospective trial is necessary to definitely demonstrate the histologic benefit of interferon therapy in the absence of loss of virus before it can be routinely recommended to push interferon in those currently considered ineligible or who suffer severe side effects. Recommendations for the management of HCV among these groups should be individualized until further study, such as with pegylated interferons, provides guidance.

Finally, and importantly, **"What is the appropriate management of patients who cannot be treated or fail to respond to treatment?"** It is incumbent upon us to remember that "management" does not necessarily mean "treatment." Management involves providing education and counseling, initiating treatment when indicated, and supplying supportive care to those for whom no clear options are available. The latter is particularly important in order to allay fears and ensure that patients are not lost to followup. At present, many patients with HCV who are not on treatment have a physical examination, blood tested for aminotransferase and AFP levels, and an abdominal US (if indicated) every 6–12 months. While these practices are conventional, few data can provide an absolute timetable for followup. It is well-known that ALT level fluctuates during the course of HCV infection and is not an adequate marker of progression of disease.[14] Although abnormalities in albumin and prothrombin time may provide more information regarding the degree of liver disease, they are not specific for liver injury, are only prognostic markers, and decline at a rate that varies from patient to patient. In addition, somewhat contradictory information exists in the literature. On the one hand, the Japanese literature recommends AFP plus ultrasound screening every 3–4 months to detect early hepatic tumors, while on the other, several studies suggest that AFP is not a sensitive surveillance test for the presence of HCC and a number of other tests including descarboxyprothrombin time, isoforms of AFP, and an isoenzyme of γGT have been advocated as alternatives.[15–17] Similarly, the pros and cons of the usefulness and timing of liver biopsy have been much debated, and intensive research in identifying surrogate serum markers of inflammation and fibrosis is ongoing. These data underscore the controversies and challenges regarding the type and schedule of tests and visits needed to appropriately follow patients with HCV.

In the meantime, it is important that physicians provide HCV-infected patients with up-to-date information about the expected course of their infection, methods of preventing transmission of HCV, and avoidance of practices (such as alcohol abuse) which may contribute to worsening liver function. In addition, we must provide *balanced* advice regarding the risks and benefits of current therapy and any new therapies as they become available. Until further data are known, it is reasonable to perform a physical exam, perform a liver panel (include PT and platelet count), and check an AFP every 6–12 months. Finally, in lieu of a serum marker of hepatic fibrosis, it may also be prudent to consider a liver biopsy every 3–5 years, particularly in those whose liver function appears to be deteriorating. While it is clear that abnormalities in these tests will be apparent before clinical symptoms appear, data to assist in determining the frequency with which they should be obtained are necessary.

Hepatitis C research has come a long way in the past 10 years. We are able to identify and quantify the virus, and in recent years, extensive investigation has identified ways to successfully treat some infected patients. Treatment of the approximately 30 percent of eligible patients with HCV has taken center stage, and a great deal of data has been generated regarding this population. However, it is clear that our obligation is to the universe of patients with HCV, not merely those who are candidates for current therapy. As physicians we must remember to provide "care," not merely "treatment." It is quintessential that we not marginalize our patients in our zeal to eradicate their disease. Solutions to the above problems are essential if we are to adequately follow and advise patients for whom therapy is not an option or has failed.

[Note: Beyond the scope of this discussion is the management of institutionalized patients infected with HCV, particularly those in correctional facilities. In many such institutions the mechanisms necessary to provide appropriate management are not available, and the cost of treatment is prohibitive. In fact, the focus on treatment of HCV rather than treatment of substance abuse or other comorbid illnesses may be counterproductive. Further study into the medical and social implications of HCV infection in institutions is needed.]

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Side Effects of Therapy and Management

Michael W. Fried, M.D.

Introduction

The side effect profile of combination therapy of standard interferon plus ribavirin is well known. In the registration trials of these agents, significant side effects were noted that resulted in discontinuation of treatment in approximately 20 percent of subjects.[1,2] The major types of side effects of combination therapy include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. Pegylated interferons (pegylated interferon alfa-2a and pegylated interferon alfa-2b) have significantly improved pharmacokinetics,[3–5] resulting in improved antiviral efficacy, that also has the potential to alter the side effect profile. This review will focus on the prevalence and management of side effects reported with the use of pegylated interferon plus ribavirin for the treatment of chronic hepatitis C.

Peginterferon Alfa-2a Plus Ribavirin

The results of a large, phase III clinical trial of peginterferon alfa-2a plus ribavirin have recently been reported in preliminary form.[6] Over 1,100 subjects were randomized to therapy with peginterferon alfa-2a plus ribavirin, peginterferon alfa-2a plus placebo, or standard interferon alfa-2b plus ribavirin. Premature withdrawal from therapy due to laboratory abnormalities or adverse events in the combination arms with either pegylated interferon alfa-2a (10 percent) or standard interferon alfa-2b (11 percent) was comparable. The most common reason for withdrawal was depression, although the rate of depression in subjects treated with peginterferon alfa-2a was lower than those treated with standard combination therapy (22 percent vs. 30 percent). Influenza-like symptoms were also lower in the peginterferon treatment groups.

Dose reductions of peginterferon alfa-2a for any adverse event were required in 32 percent in the combination arm. Laboratory abnormalities such as anemia, neutropenia, and thrombocytopenia were the most frequent indications for dose reductions. Thus, approximately 25 percent of participants required at least one dose reduction (temporary or permanent) for laboratory abnormalities during therapy. The frequency of ribavirin dose reduction for anemia was similar in the combination arms of the study. The frequency of dose reduction for neutropenia was greater in the peginterferon combination arm compared to standard interferon (20 percent vs. 5 percent). Thrombocytopenia was also more common in the peginterferon arms. However, only a minority of patients discontinued therapy due to laboratory abnormalities in the two combination arms (peginterferon + ribavirin = 3 percent vs. standard interferon plus ribavirin = 1 percent).

Peginterferon Alfa-2b Plus Ribavirin

In a large, phase III study that compared the antiviral efficacy of two different regimens of peginterferon alfa-2b plus ribavirin to standard interferon alfa-2b plus ribavirin,[7] premature

withdrawal from therapy due to an adverse event occurred in 14 percent of participants treated with the higher dose of peginterferon. Discontinuation of therapy due to neutropenia (~1 percent) or anemia was very uncommon. Dose reductions for any adverse event occurred in 42 percent of patients treated with the higher dose peginterferon alfa-2b plus ribavirin compared to 34 percent treated with standard interferon and ribavirin. Dose reduction due to neutropenia was also more common in the higher dose combination (18 percent) than in the low dose pegylated (10 percent) or the standard interferon combination arms (8 percent).

Few differences were noted in the side effect profile in the pegylated combination arms compared to those seen with standard interferon plus ribavirin. The incidence of depression was similar in all treatment arms (~30 percent). The increase of several flu-like symptoms over standard therapy was attributed to the higher dose of interferon provided by the pegylated preparation. Injection site reaction, generally mild, was also noted to be more common in those receiving peginterferon alfa-2b (58 percent) compared to the standard interferon alfa-2b (36 percent).

Management of Side Effects

General strategies for management of side effects of combination therapy have been previously reviewed and are applicable to the newer agents.[8] Before starting treatment, patient education about expectations and self-management techniques are most beneficial. Regular followup visits during therapy and a supportive environment will permit early detection and intervention for developing adverse events and will also encourage patient adherence to the medication regimen.

Depression is a frequent and often dose-limiting side effect of combination therapy with pegylated interferon and ribavirin. The mechanism of interferon-associated depression remains largely speculative. Directed questioning of the patient and significant others, when available, about the presence and severity of depression is warranted. Treatment should be discontinued immediately in patients with suicidal ideation and, for patients judged to be in potential danger, immediate referral should be made to a mental health professional. Antidepressants, particularly selective serotonin-reuptake inhibitors, are prescribed frequently for less severe depression associated with antiviral therapy. Prophylactic paroxetine, evaluated in patients treated with high-dose interferon alfa-2b for melanoma, was shown to minimize depressive symptoms and decrease the rate of interferon discontinuation compared to placebo.[9] However, prophylactic strategies could result in inappropriate use of these agents in the 70–80 percent of patients that do not develop significant depression while on combination therapy for hepatitis C. Thus, additional information is needed concerning the mechanisms of interferon-associated depression and the optimal treatment regimen that will minimize disruptions to antiviral therapy.

Anemia, thrombocytopenia, and especially, neutropenia occur regularly in patients treated with peginterferon and ribavirin. To date, management of hematologic abnormalities in all phase III clinical trials has relied upon dose reductions of study medications according to predetermined criteria. This has proven to be a safe and effective approach to management; hemoglobin, absolute neutrophil and platelet counts improve quickly so that discontinuation of therapy is rarely necessary. Nevertheless, the possibility that adherence to study medications may

affect sustained virological response has encouraged evaluation of erythropoietin and granulocyte stimulating factors as adjunctive therapies to minimize dose reductions of interferon and ribavirin. Preliminary data suggest that the dose of ribavirin may be maintained with epoietin alfa.[10] However, no study thus far has demonstrated that the use of stimulating factors to maintain full doses of interferon and ribavirin will improve sustained virological response. Furthermore, the incidence of serious sequelae associated with hematologic abnormalities appears to be low. Thus, these adjunctive agents cannot be routinely recommended as treatment for the hematologic abnormalities induced by combination therapy for hepatitis C. Additional studies are required to better understand the consequences of neutropenia in the patient with chronic hepatitis C and to determine whether lower levels of neutropenia can be safely tolerated. Detailed investigations of the relationship between dose reduction on outcome and prospective trials of alternative methods for managing hematologic abnormalities with growth factors are necessary.

In summary, no unique or unexpected side effects have been noted with the administration of pegylated interferons plus ribavirin in two large phase III trials of these agents. Hematologic abnormalities requiring dose reductions may be more common with the newer agents. Additional emphasis on improving patient management strategies is warranted.

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Future Therapy of Hepatitis C

John G. McHutchison, M.D.

Introduction

Although current therapies are effective in more than half of all treated patients, therapy is costly, associated with significant morbidity, requires substantial commitment from the patient and medical staff, and is not suitable for all patients. Thus, there is an important need for more effective therapies, and this remains a priority in terms of continued research endeavours. The lack of an effective cell culture system and small animal model for HCV infection has hampered the development and discovery of alternative effective small molecules or vaccines. Nevertheless, the ideal therapy for patients with chronic hepatitis C would be cost-effective, be orally bioavailable, have an acceptable side effect profile, and be effective in the majority of patients. Such therapies are probably unlikely to be developed in the near future. Therapies in current development and/or in human clinical trials will be discussed.

Adjuvant Agents That May Be Added to Current Regimens

Alternative Interferons or Interferon Inducing Agents

The development of alternative type 1 interferon compounds or methods of delivering longer acting preparations with theoretically different pharmacokinetic profiles may lead to the availability of alternate interferon preparations. Whether these will improve or enhance sustained response rates or side effect profiles in combination with ribavirin or other agents in larger clinical trials is unknown and is currently under early stage clinical investigation. Oral interferon inducing agents are also in pre-clinical trials, and probably phase I human development will occur in late 2002.

IMPDH Inhibitors. The development of compounds which specifically inhibit inosine 5′ monophosphate dehydrogenase (IMPDH) may provide an alternative for patients with chronic hepatitis C when combined with interferon. This enzyme, which is also inhibited by ribavirin and mycophenolate, is essential for modulation of host cellular pathways and has antiviral and immunomodulatory effects. Phase I and II clinical trials in patients with chronic hepatitis C have shown one such agent (VX-497) to be safe, but with no observable antiviral effect when given alone. As in the initial ribavirin monotherapy studies, ALT reductions were also noted in some patients. A subsequent phase II, randomized, double-blind study of VX-497 combined with interferon in treatment naïve patients for 4 weeks indicated safety in combination with interferon, but no enhancement of antiviral activity. Further development of more potent and specific IMPDH inhibitors will require randomized controlled clinical trials to determine their efficacy and future place in the management of patients with chronic hepatitis C.

Alternative Ribavirin-Like Drugs. Other agents similar to ribavirin that bias the immune response toward a type 1 profile are in development. These drugs will further test the hypothesis

that a significant component of the benefit of ribavirin is by its action as a type 1 cytokine enhancer. Levovirin, the l-isomer of ribavirin, is associated with lesser degrees of hemolytic anemia, appears safe in animal studies, and has been well tolerated in phase I dose finding studies in healthy volunteers. Viramidine, a ribavirin prodrug, also produces less hemolysis, is converted rapidly to ribavirin in vivo, has a three- to sixfold longer residence time in the liver, and is less concentrated in peripheral blood red cells compared to ribavirin. The safety, utility and future development of these and other similar agents will need to be established in larger-scale clinical trials in combination with alpha interferons.

Other Immunomodulators

Histamine. Histamine dihydrochloride, through binding of H2 receptors on phagocytic cells, disrupts NADPH-oxidase responsible for the production of reactive oxygen species and is also an immunomodulator acting on NK and T cells. This compound has been tested in combination with interferon in certain malignancies and in initial pilot studies in patients with hepatitis C. In two phase II studies where histamine dihydrochloride was administered to patients along with interferon, or in combination with interferon and ribavirin, the data suggest there may be benefit in terms of end of treatment and sustained response rates. An ongoing European, multinational trial is currently evaluating the safety and efficacy of peginterferon plus ribavirin vs. peginterferon plus ribavirin plus histamine injections in hepatitis C patients.

Molecular Based Therapies

Hepatitis C Specific Viral Enzyme Inhibitors

Based upon current knowledge of the structural biology and actions of HCV specific enzymes during viral replication, many groups are pursuing the development of compounds that specifically inhibit enzymes critical to the HCV life cycle. There are three initial and important virus specific targets for antiviral drug development including the HCV protease, polymerase, and helicase enzymes. The efficacy of these compounds is now being evaluated using the HCV replicon model system, and promising compounds will undergo testing in animals for oral bioavailability and toxicity. The structure of many potential inhibitors has been described, and a number of early phase I trials are being undertaken with HCV specific protease and polymerase inhibitors in chronic hepatitis C patients.

Barriers to the development of these agents are numerous, and include the shallow protease binding cleft, viral drug resistance, and the fact that such agents will be required to have activity profiles against a broad range of HCV genotypes. Also, the importance of combination therapy to multiple enzyme targets has been demonstrated in the HIV clinical setting to avoid the selection of resistant viral strains. As such, multiple targets of this class will be required in order to reduce or eliminate drug resistant HCV quasispecies, and assays to detect viral resistance patterns must be established.

Antisense Oligonucleotides

HCV specific antisense oligonucleotides, short sequences of 15–40 nucleotides stabilized to protect these molecules against cellular nuclease degradation, can hybridize to and prevent translation of viral RNA and thus inhibit disease causing protein expression. A 20 nucleotide phosphorothioate oligonucleotide with a sequence complementary to the HCV translation initiation region (ISIS 14803) is currently undergoing phase I and II clinical trials in patients who have failed to respond to available antiviral therapies. Some patients have had viral load reductions of $\geq$ 1 log in HCV RNA after 28 days of therapy. For unexplained reasons these viral load changes are sometimes, but not always, associated with asymptomatic but significant ALT elevations. The efficacy and safety of this compound is now being evaluated in phase II studies of 12 weeks' duration in previous nonresponders to other antiviral therapies.

HCV Specific Ribozymes

Synthetic nuclease resistant ribozymes designed to cleave the hepatitis C virus IRES are currently in phase II clinical trials. These stabilized ribozymes contain modified nucleotides and phosphorothioate linkages and are efficiently taken up by the liver. In preliminary cell culture studies, these ribozymes inhibited viral replication in a dose dependent fashion, and this effect was potentiated by interferon. Phase II trials administering these HCV specific ribozymes, alone or in combination with interferon for 12 weeks' duration, are currently in progress.

While these newer small molecule approaches provide hope and excitement for the treatment of HCV infected patients, many further studies will be necessary to determine the safety and efficacy of these approaches, their effect on liver histology, and the mechanisms of any antiviral effects, and to evaluate whether such agents will need to be administered in combination with our available antiviral therapies to prevent the development of resistance.

Strategies to Minimize Hepatic Fibrosis

Interferon Gamma. Interferon γ is an antifibrotic cytokine in murine and human hepatic stellate cells, is an immunomodulatory cytokine, and has HCV specific antiviral activiy. A phase II randomized, double-blind, multicenter trial to determine the antifibrotic efficacy of interferon gamma 1b is currently underway in patients with hepatic fibrosis due to hepatitis C and compensated cirrhosis, using a histologic primary end point.

Cellular immuno therapy. Cytotoxic T lymphocytes play an important role in viral clearance and immunological memory in chronic hepatitis B, and likewise it is thought that a strong, multispecific directed CTL response contributes to HCV clearance in those individuals who are fortunate enough to spontaneously resolve HCV infection. Various groups have created vaccines containing HCV specific viral epitopes that are recognized by cytotoxic T-cells. Whether these agents can be successfully used as potential vaccines in the primary prophylaxis setting, or in the setting of a therapeutic vaccine to modify the host immune response in patients with chronic hepatitis C infection is currently unknown. One such agent is currently in early phase human trials.

Conclusion

Although many of these future strategies are currently in development, it will require a number of years before the safety, short- and long-term efficacy, clinical value, and appropriate setting for each of these agents alone and in combination regimens is established. For these reasons, it is unlikely that many of these newer therapies, even if proven to be effective, will be available for routine clinical use within the next 3–5 years.

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