Chronic Hepatitis C:
Current Disease Management

National Institute of Diabetes and Digestive and Kidney Diseases

NATIONAL INSTITUTES OF HEALTH

The hepatitis C virus (HCV) is one of the most important causes of chronic liver disease in the United States. It accounts for about 15 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and up to 50 percent of cirrhosis, end-stage liver disease, and liver cancer. Of the U.S. population, 1.6 percent, or an estimated 4.1 million Americans, have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. Hepatitis C causes an estimated 10,000 to 12,000 deaths annually in the United States.

A distinct and major characteristic of hepatitis C is its tendency to cause chronic liver disease in which the liver injury persists for a prolonged period if not for life. About 75 percent of patients with acute hepatitis C ultimately develop chronic infection.

Chronic hepatitis C varies greatly in its course and outcome. At one end of the spectrum are infected persons who have no signs or symptoms of liver disease and have completely normal levels of serum enzymes, the usual blood test results that indicate liver disease. Liver biopsy usually shows some degree of injury to the liver, but the extent is usually mild, and the overall prognosis may be good. At the other end of the spectrum are patients with severe hepatitis C who have symptoms, high levels of the virus (HCV RNA) in serum, and elevated serum enzymes, and who ultimately develop cirrhosis and end-stage liver disease. In the middle of the spectrum are many patients who have few or no symptoms, mild to moderate elevations in liver enzymes, and an uncertain prognosis.

Chronic hepatitis C can cause cirrhosis, liver failure, and liver cancer. Researchers estimate that at least 20 percent of patients with chronic hepatitis C develop cirrhosis, a process that takes at least 10 to 20 years. Liver failure from chronic hepatitis C is one of the most common reasons for liver transplants in the United States. After 20 to 40 years, a small percentage of patients develop liver cancer. Hepatitis C is the cause of about half of cases of primary liver cancer in the developed world. Men, alcoholics, patients with cirrhosis, people over age 40, and those infected for 20 to 40 years are at higher risk of developing HCV-related liver cancer.

Risk Factors and Transmission

HCV is spread primarily by contact with infected blood and blood products. Blood transfusions and the use of shared, unsterilized, or poorly sterilized needles, syringes and injection equipment or paraphernalia have been the main routes of the spread of HCV in the United States. With the introduction in 1991 of routine blood screening for HCV antibody and improvements in the test in mid-1992, transfusion-related hepatitis C has virtually disappeared. At present, injection drug use is the most common risk factor for contracting the infection.

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However, some patients who acquire hepatitis C do not have a recognized risk factor or known exposure to infected blood or to drug use.

The most common risk factors for acquiring hepatitis C are

- injecting drugs, including having used injection drugs only once many years ago

- having a blood transfusion before June 1992, when sensitive tests for anti-HCV were introduced for blood screening

- receiving clotting factor concentrates (such as anti-hemophilic factor) before 1987, when effective means to inactive HCV were introduced

- hemodialysis for kidney failure

- birth to an HCV-infected mother

- suffering a needle-stick accident from a person with hepatitis C

Other risk factors that have a slightly increased risk for hepatitis C are

- having sex with someone with hepatitis C or having multiple sex partners

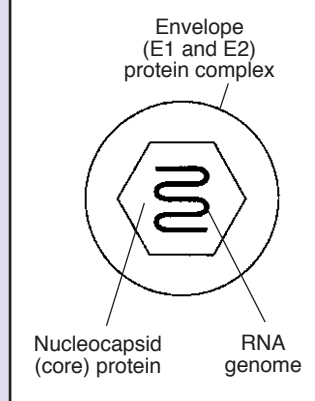- intranasal use of cocaine using shared equipment or paraphernalia

Maternal-Infant Transmission

Maternal-infant transmission is not common. In most studies, less than 5 percent of infants born to HCV-infected mothers become infected. The disease in newborns is usually mild and free of symptoms. The risk of maternal-infant spread rises with the amount of virus in the mother's blood, if the mother also has human immunodeficiency virus (HIV) infection, or if there are complications of delivery such as early rupture of membranes and fetal monitoring. Breast-feeding has not been linked to the spread of HCV.

Sexual Transmission

Sexual transmission of hepatitis C between monogamous partners appears to be uncommon. Surveys of spouses and monogamous sexual partners of patients with hepatitis C show that fewer than 5 percent are infected with HCV, and many of these have other risk factors for this infection. Spread of hepatitis C to a spouse or partner in stable, monogamous relationships occurs in less than 1 percent of partners per year. For these reasons, changes in sexual practices are not recommended for monogamous patients. Testing sexual partners for anti-HCV can help with patient counseling. People with multiple sex partners should be advised to follow safe sex practices, which should protect against hepatitis C as well as hepatitis B, HIV, and other sexually transmitted diseases.

The Hepatitis C Virus

HCV Viral Components

Envelope
(E1 and E2)
protein complex

Nucleocapsid
(core) protein

RNA
genome

HCV is a small (40 to 60 nanometers in diameter), enveloped, single-stranded RNA virus of the family Flaviviridae and genus hepacivirus. Because the virus mutates rapidly, changes in the envelope proteins may help it evade the immune system. There are at least six major genotypes and more than 50 subtypes of HCV. The different genotypes have different geographic distributions. Genotypes 1a and 1b are the most common in the United States (about 75 percent of cases). Genotypes 2 and 3 are present in only 10 to 20 percent of patients. There is little difference in the severity of disease or outcome of patients infected with different genotypes. However, patients with genotypes 2 and 3 are more likely to respond to interferon treatment.

Sporadic Transmission

Sporadic transmission, when the source of infection is unknown, is the basis for about 10 percent of acute hepatitis C cases and for 30 percent of chronic hepatitis C cases. These cases are usually referred to as sporadic or community-acquired infections. These infections may have come from exposure to the virus from cuts, wounds, or medical injections or procedures.

Unsafe Injection Practices

In many areas of the world, unsafe injection practices in the delivery of health care are an important and common cause of hepatitis C (and hepatitis B as well). Use of inadequately sterilized equipment, reuse of needles and syringes, and inadvertent contamination of medical infusions are unfortunately well-documented causes of transmission of hepatitis C. Careful attention to universal precautions and injection techniques should prevent this type of spread. In the United States, multiple-use vials are a frequent culprit in leading to medical-care linked spread of hepatitis C.

Clinical Symptoms and Signs

Many people with chronic hepatitis C have no symptoms of liver disease. If symptoms are present, they are usually mild, nonspecific, and intermittent. They may include

- fatigue

- mild right-upper-quadrant discomfort or tenderness ("liver pain")

- nausea

- poor appetite

- muscle and joint pains

Similarly, the physical exam is likely to be normal or show only mild enlargement of the liver or tenderness. Some patients have vascular spiders or palmar erythema.

Clinical Features of Cirrhosis

Once a patient develops cirrhosis or if the patient has severe disease, symptoms and signs are more prominent. In addition to fatigue, the patient may complain of muscle weakness, poor appetite, nausea, weight loss, itching, dark urine, fluid retention, and abdominal swelling.

Physical findings of cirrhosis may include

- enlarged liver

- enlarged spleen

- jaundice

- muscle wasting

- excoriations (scratches or abrasions on the skin)

- ascites (fluid-filled belly)

- ankle swelling

Extrahepatic Manifestations

Complications that do not involve the liver develop in 1 to 2 percent of people with hepatitis C; the most common is cryoglobulinemia, which is marked by

- skin rashes, such as purpura, vasculitis, or urticaria

- joint and muscle aches

- kidney disease

- neuropathy

- cryoglobulins, rheumatoid factor, and low-complement levels in serum

Other complications of chronic hepatitis C are

- glomerulonephritis

- porphyria cutanea tarda

Diseases that are less well documented to be related to hepatitis C are

- seronegative arthritis

- keratoconjunctivitis sicca (Sjögren's syndrome)

- non-Hodgkin's type, B-cell lymphomas

- fibromyalgia

- lichen planus

Serologic Tests

Enzyme Immunoassay

Persons suspected to have hepatitis C should be tested for anti-HCV as an initial screening test. Anti-HCV is detected by enzyme immunoassay (EIA). The third-generation test (EIA-3) used today is more sensitive and specific than previous ones. As with all enzyme immunoassays, however, false-positive results are occasionally a problem with the EIA-3. Additional or confirmatory testing is often helpful.

The best approach to confirm the diagnosis of hepatitis C is to test for HCV RNA using a sensitive assay such as polymerase chain reaction (PCR) or transcription-mediated amplification (TMA). The presence of HCV RNA in serum indicates an active infection.

Testing for HCV RNA is also helpful in patients in whom EIA tests for anti-HCV are unreliable. For instance, immunocompromised patients may test negative for anti-HCV despite having HCV infection because they may not produce enough antibodies for detection with EIA. Likewise, patients with acute hepatitis may test negative for anti-HCV when first tested. Antibody is present in almost all patients by 1 month after onset of acute illness; thus, patients with acute hepatitis who initially test negative may need follow-up testing. In these situations, HCV RNA is usually present and confirms the diagnosis.

Recombinant Immunoblot Assay

Immunoblot assays can be used to confirm anti-HCV reactivity. These tests are also called "Western blots"; serum is incubated on nitrocellulose strips on which four recombinant viral proteins are blotted. Color changes indicate that antibodies are adhering to the proteins. An immunoblot is considered positive if two or more proteins react and is considered indeterminate if only one positive band is detected. In some clinical situations, confirmatory testing by immunoblotting is helpful, such as for the person with anti-HCV detected by EIA who tests negative for HCV RNA. The EIA anti-HCV reactivity could represent a false-positive reaction, recovery from hepatitis C, or continued virus infection with levels of virus too low to be detected (the last occurs only rarely when sensitive PCR or TMA assays are used). If the immunoblot test for anti-HCV is positive, the patient has most likely recovered from hepatitis C and has persistent antibody. If the immunoblot test is negative, the EIA result was probably a false positive.

Immunoblot tests are routine in blood banks when an anti-HCV-positive sample is found by EIA. Immunoblot assays are highly specific and valuable in verifying anti-HCV reactivity. Indeterminate tests require further follow-up testing, including attempts to confirm the specificity by repeat testing for HCV RNA.

Direct Assays for HCV RNA

PCR and TMA amplification can detect low levels of HCV RNA in serum. Testing for HCV RNA is a reliable way of demonstrating that hepatitis C infection is present and is the most specific test for infection. Testing for HCV RNA is particularly useful when aminotransferase levels are normal or only slightly elevated, when anti-HCV is not present, or when several causes of liver disease are possible. This method also helps diagnose hepatitis C in people who are immunosuppressed, have recently had an organ transplant, or have chronic renal failure. Currently available PCR assays will detect HCV RNA in serum down to a lower limit of 50 to 100 copies per milliliter (mL), which is equivalent to 25 to 50 international units (IU). A slightly more sensitive TMA test has recently become available. Almost all patients with chronic hepatitis C will test positive by these assays.

Biochemical Indicators of Hepatitis C Virus Infection

- In chronic hepatitis C, increases in the alanine and aspartate amino-transferases range from zero to 20 times (but usually less than five times) the upper limit of normal.

- Alanine aminotransferase (ALT) levels are usually higher than aspartate aminotransferase (AST) levels, but that finding may be reversed in patients who have cirrhosis.

- Alkaline phosphatase and gamma glutamyl transpeptidase are usually normal. If elevated, they may indicate cirrhosis.

- Low platelet and white blood cell counts and raised levels of serum globulins (including immunoglobulins and rheumatoid factor) are frequent in patients with severe fibrosis or cirrhosis, providing clues to the presence of advanced disease.

- The enzymes lactate dehydrogenase and creatine kinase are usually normal.

- Albumin levels, bilirubin, and prothrombin time are normal until late-stage disease.

- Iron and ferritin levels may be slightly elevated.

Quantification of HCV RNA in Serum

Several methods are available for measuring the concentration or level of virus in serum, which is an indirect assessment of viral load. These methods include a quantitative PCR and a branched DNA (bDNA) test. Unfortunately, these assays are not well standardized, and different methods from different laboratories can provide different results on the same specimen. In addition, serum levels of HCV RNA can vary spontaneously by 3- to 10-fold over time. Nevertheless, when performed carefully, quantitative assays provide important insights into the nature of hepatitis C. Most patients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 (10^5) and 10,000,000 (10^7) copies per mL. Expressed as IU, these averages are 50,000 to 5 million IU.

Viral levels as measured by HCV RNA do not correlate with the severity of the hepatitis or with a poor prognosis (as in HIV infection); but viral load does correlate with the likelihood of a response to antiviral therapy. Rates of response to a course of peginterferon and ribavirin are higher in patients with low levels of HCV RNA. There are several definitions of a "low level" of HCV RNA, but the usual definition is below 800,000 IU ($\sim$ 2 million copies) per mL.

In addition, monitoring HCV RNA levels during the early phases of treatment may provide early information on the likelihood of a response. Yet because of the short-comings of the current assays for HCV RNA level, these tests are not always reliable guides to therapy.

Genotyping and Serotyping of HCV

There are six known genotypes and more than 50 subtypes of hepatitis C. The genotype is helpful in defining the epidemiology of hepatitis C. More important, knowing the genotype or serotype (genotype-specific antibodies) of HCV is helpful in making recommendations and counseling regarding therapy. Patients with genotypes 2 and 3 are two to three times more likely to respond to interferon-based therapy than patients with genotype 1. Furthermore, when using combination therapy, the recommended dose and duration of treatment depend on the genotype. For patients with genotypes 2 and 3, a 24-week course of combination treatment using peginterferon and 800 milligrams (mg) of ribavirin daily is adequate, whereas for patients with genotype 1, a 48-week course and full dose of ribavirin (1,000 to 1,200 mg daily) is recommended. For these reasons, testing for HCV genotype is clinically important. Once the genotype is identified, it need not be tested again; genotypes do not change during the course of infection.

Normal Serum ALT Levels

Up to 40 percent of patients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions. In this and other situations in which the diagnosis of chronic hepatitis C may be questioned, the diagnosis should be confirmed by testing for HCV RNA. The presence of HCV RNA indicates that the patient has ongoing viral infection despite normal ALT levels.

Liver Biopsy

Liver biopsy is not necessary for diagnosis but is helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage. Hematoxylin and eosin stains and Masson's trichrome stain are used to grade the amount of necrosis and inflammation and to stage the degree of fibrosis. Specific immunohistochemical stains for HCV have not been developed for routine use. Liver biopsy is also helpful in ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.

HCV causes the following changes in liver tissue:

- Necrosis and inflammation at the edge of the portal areas, so-called "piecemeal necrosis" or "interface hepatitis"

- Necrosis of hepatocytes and focal inflammation in the liver parenchyma

- Inflammatory cells in the portal areas ("portal inflammation")

- Fibrosis may exist in an early stage, being confined to the portal tracts, an intermediate stage consisting of expansion of the portal tracts and bridging between portal areas or to the central area, or a late stage of frank cirrhosis characterized by architectural disruption of the liver with fibrosis and regeneration. Several scales are used to stage fibrosis. One common classification is a scale from 0 to 4 where stage 0 indicates no fibrosis; stage 1 indicates enlargement of the portal

areas by fibrosis; stage 2 indicates fibrosis extending out from the portal areas with rare bridges between portal areas; stage 3 indicates many bridges of fibrosis that link up portal and central areas of the liver; and stage 4 indicates cirrhosis.

By assigning scores for severity, grading and staging of hepatitis are helpful in managing patients with chronic hepatitis. The degree of inflammation and necrosis can be assessed as none, minimal, mild, moderate, or severe. The degree of fibrosis can be similarly assessed. Scoring systems are particularly helpful in clinical studies on chronic hepatitis.

Noninvasive Tests

While liver biopsy is considered the "gold standard" for assessing the severity of liver disease, it is not always accurate and has several shortcomings. Liver biopsy can under- or over-estimate the severity of hepatitis C, particularly if the biopsy is small and if it is not read by a knowledgeable expert. In addition, liver biopsy is an invasive procedure that is expensive and not without complications. At least 20 percent of patients have pain requiring medications after liver biopsy. Rare complications include puncture of another organ, infection, and bleeding. Significant bleeding after liver biopsy occurs in one out of 100 to one out of 1,000 cases, and deaths are reported in one out of 5,000 to one out of 10,000 cases. Obviously, noninvasive means of grading and staging liver disease would be very helpful.

ALT levels, particularly if tested over an extended period, are reasonably accurate reflections of disease activity. Thus, patients with repeatedly normal ALT levels usually have mild inflammation and liver cell injury on liver biopsy. Furthermore, patients who maintain ALT levels above five times the upper limit of normal usually have marked inflammatory activity. But for the majority of patients with mild to moderate ALT elevations, the actual level is not very predictive of liver biopsy findings.

More important is a means to stage liver disease and measure fibrosis short of liver biopsy. Unfortunately, serum tests are not reliable in predicting fibrosis, particularly earlier stages (0, 1, and 2). When patients develop bridging (stage 3) fibrosis and cirrhosis (stage 4), serum tests may be helpful. The "danger signals" that suggest the presence of advanced fibrosis include an aspartate aminotransferase (AST) that is higher than ALT (reversal of the ALT/AST ratio), a high gamma glutamyl transpeptidase or alkaline phosphatase, a decrease in platelet count (which is perhaps the earliest change), elevations in serum globulins, and, of course, abnormal bilirubin, albumin, or prothrombin time. Physical findings of a firm liver, or enlarged spleen or prominent spider angionata or palmar erythema, are also danger signals. While none of these findings are completely reliable, their presence should raise the suspicion of significant fibrosis and lead to evaluation for treatment sooner rather than later.

Recently, x-ray and imaging studies have been developed that may be able to separate different degrees of fibrosis in the liver. At present, these techniques are experimental and of unproven accuracy, particularly in detecting early stages of fibrosis. The most promising technique is "elastrography," in which sound or magnetic waves are passed through the liver and the speed with which they return is measured, which provides an index of the elasticity and stiffness of the liver. Liver stiffness is used as an indirect measure of liver fibrosis. Most importantly, measuring the relative stiffness of the liver over time may provide a noninvasive way to monitor the development of fibrosis and help guide recommendations for when therapy should be recommended. Ultrasound elastrography is currently under evaluation for its reliability in measuring the degree of fibrosis in the liver in patients with hepatitis C. Ultimately, elastrography may be able to replace liver biopsy as a way of monitoring the progression of disease in chronic hepatitis C.

Diagnosis

Hepatitis C is most readily diagnosed when serum aminotransferases are elevated and anti-HCV is present in serum. The diagnosis is confirmed by the finding of HCV RNA in serum.

Acute Hepatitis C

Acute hepatitis C is diagnosed in persons who have symptoms such as jaundice, fatigue, and nausea, together with marked increases in serum ALT (usually greater than 10-fold elevation), and the presence of anti-HCV or *de novo* development of anti-HCV.

Diagnosis of acute disease can be problematic because anti-HCV is not always present when the patient develops symptoms and sees the physician. In 30 to 40 percent of patients, anti-HCV is not detected until 2 to 8 weeks after onset of symptoms. In this situation, testing for HCV RNA is helpful, as this marker is present even before the onset of symptoms and lasts through the acute illness. Another approach to diagnosis of acute hepatitis C is to repeat the anti-HCV testing a month after onset of illness. Of course, a history of an acute exposure is also helpful in suggesting the diagnosis.

Chronic Hepatitis C

Chronic hepatitis C is diagnosed when anti-HCV is present and serum aminotransferase levels remain elevated for more than 6 months. Testing for HCV RNA (by PCR) confirms the diagnosis and documents that viremia is present; almost all patients with chronic infection will have the viral genome detectable in serum by PCR.

Diagnosis is problematic in patients who cannot produce anti-HCV because they are immunosuppressed or immunoincompetent. Thus, HCV RNA testing may be required for patients who have a solid-organ transplant, are on dialysis, are taking corticosteroids, or have agammaglobulinemia. Diagnosis is also difficult in patients with anti-HCV who have another form of liver disease that might be responsible for the liver injury, such as alcoholism, iron overload, or autoimmunity. In these situations, the anti-HCV may represent a false-positive reaction, previous HCV infection, or mild hepatitis C occurring on top of another liver condition. HCV RNA testing in these situations helps confirm that hepatitis C is contributing to the liver problem.

Differential Diagnosis

The major conditions that can be confused clinically with chronic hepatitis C include

- autoimmune hepatitis
- chronic hepatitis B and D
- alcoholic hepatitis
- nonalcoholic steatohepatitis (fatty liver)
- sclerosing cholangitis
- Wilson disease
- alpha-1-antitrypsin-deficiency-related liver disease
- drug-induced liver disease

Treatment

Alpha Interferon

The therapy for chronic hepatitis C has evolved steadily since alpha interferon was first approved for use in this disease more than 10 years ago. At the present time, the optimal regimen appears to be a 24- or 48-week course of the combination of pegylated alpha interferon and ribavirin.

Alpha interferon is a host protein that is made in response to viral infections and has natural antiviral activity. Recombinant forms of alpha interferon have been produced, and several formulations (alfa-2a, alfa-2b, consensus interferon) are available as therapy for hepatitis C. These standard forms of interferon, however, are now being replaced by pegylated interferon (peginterferon).

Peginterferon is alpha interferon that has been modified chemically by the addition of a large inert molecule of polyethylene glycol. Pegylation changes the uptake, distribution, and excretion of interferon, prolonging its half-life. Peginterferon can be given once weekly and provides a constant level of interferon in the blood, whereas standard interferon must be given several times weekly and provides intermittent and fluctuating levels. In addition, peginterferon is more active than standard interferon in inhibiting HCV and yields higher sustained response rates with similar side effects. Because of its ease of administration and better efficacy, peginterferon has replaced standard interferon both as monotherapy and as combination therapy for hepatitis C.

Ribavirin

Ribavirin is an oral antiviral agent that has activity against a broad range of viruses. By itself, ribavirin has little effect on HCV, but adding it to interferon increases the sustained response rate by two- to three-fold. For these reasons, combination therapy is now recommended for hepatitis C, and interferon monotherapy is applied only when there are specific reasons not to use ribavirin.

Combination Therapy

Combination therapy leads to rapid improvements in serum ALT levels and disappearance of detectable HCV RNA in up to 70 percent of patients. However, long-term improvement in hepatitis C occurs only if HCV RNA disappears during therapy and stays undetectable once therapy is stopped. Among patients who become HCV RNA negative during treatment, some will relapse when therapy is stopped. The relapse rate is lower in patients treated with combination therapy compared with monotherapy. Thus, a 48-week course of combination therapy using peginterferon and ribavirin yields a sustained response rate of about 55 percent. A similar course of peginterferon monotherapy yields a sustained response rate of only 35 percent. A response is considered "sustained" if HCV RNA remains undetectable for 6 months or more after stopping therapy.

Dosing

Two forms of peginterferon have been developed and studied in large clinical trials: peginterferon alfa-2a (Pegasys: Hoffman La Roche, Nutley, NJ) and peginterferon alfa-2b (Pegintron: Schering-Plough Corporation, Kenilworth, NJ). These two products are roughly equivalent in efficacy and safety, but have different dosing regimens.

- Peginterferon alfa-2a is given subcutaneously in a fixed dose of 180 micrograms (mcg) per week.

- Peginterferon alfa-2b is given subcutaneously weekly in a weight-based dose of 1.5 mcg per kilogram (kg) per week (thus in the range of 75 to 150 mcg per week).

Ribavirin is an oral medication, given twice a day in 200-mg capsules for a total daily dose based upon body weight. The standard dose of ribavirin is 1,000 mg for patients who weigh less than 75 kg (165 pounds) and 1,200 mg for those who weigh more than 75 kg. In certain situations, an 800-mg dose (400 mg twice daily) is recommended (see next page).

Duration

The optimal duration of treatment varies depending on whether interferon monotherapy or combination therapy is used, as well as by HCV genotype. For patients treated with peginterferon monotherapy, a 48-week course is recommended, regardless of genotype. For patients treated with combination therapy, the optimal duration of treatment depends on viral genotype. Patients with genotypes 2 and 3 have a high rate of response to combination treatment (70 to 80 percent), and a 24-week course of combination therapy yields results equivalent to those of a 48-week course. In contrast, patients with genotype 1 have a lower rate of response to combination therapy (40 to 45 percent), and a 48-week course yields a significantly better sustained response rate. Again, because of the variable responses to treatment, testing for HCV genotype is clinically useful when considering starting combination therapy.

In addition, the optimal dose of ribavirin appears to vary depending on genotype. For patients with genotypes 2 or 3, a dose of 800 mg daily appears adequate. For patients with genotype 1, the full dose of ribavirin (1,000 or 1,200 mg daily depending on body weight) appears to be needed for an optimal response.

There is little information on the optimal regimen of peginterferon and ribavirin for patients with the rare genotypes 4, 5, and 6. These patients should probably receive the regimen of peginterferon and ribavirin that is recommended for genotype 1.

Many attempts have been made to identify patients who have a rapid response to treatment and who might be able to stop peginterferon and ribavirin early and be spared the further expense and side effects of prolonged therapy. Patients who test HCV RNA negative within 4 weeks of starting therapy are considered "rapid responders." In several studies, rapid responders with genotypes 2 and 3 have been found to be able to stop therapy after 12 to 16 weeks (12 to 8 weeks early) and still achieve a high rate of response. Similarly, rapid responders with genotype 1 may be able to stop therapy at 24 weeks (24 weeks early) and achieve an excellent response rate. The consequence of early stopping, however, is a higher relapse rate and this approach of abbreviating therapy in rapid responders must be individualized based upon tolerance.

Who should be treated?

Patients with anti-HCV, HCV RNA, elevated serum aminotransferase levels, and evidence of chronic hepatitis on liver biopsy, and with no contraindications, should be offered therapy with the combination of peginterferon and ribavirin. The National Institutes of Health Consensus Development Conference Panel recommended that therapy for hepatitis C be limited to those patients who have histological evidence of progressive disease. Thus, the panel recommended that all patients with fibrosis or moderate to severe degrees of inflammation and necrosis on liver biopsy should be treated and that patients with less severe histological disease be managed on an individual basis. Patient selection should not be based on the presence or

absence of symptoms, the mode of acquisition, the genotype of HCV RNA, or serum HCV RNA levels.

Between 30 and 40 percent of patients with chronic hepatitis C have normal serum aminotransferase levels. These patients usually have mild disease that is unlikely to progress. Nevertheless, such patients may wish to be treated and, indeed, response rates to peginterferon and ribavirin appear to be independent of serum aminotransferase levels. Patients who prefer not to be treated at present should be monitored as advances in the field may ultimately lead to more effective and better tolerated therapies. When questions arise regarding treatment, liver biopsy can be helpful in documenting the level of disease activity and liver fibrosis and thus the advisability of waiting for future improvements in therapy.

Patients with cirrhosis can be offered therapy if they do not have signs of decompensation, such as ascites, persistent jaundice, wasting, variceal hemorrhage, or hepatic encephalopathy. However, combination therapy has not been shown to improve survival or the ultimate outcome in patients with pre-existing cirrhosis.

The role of peginterferon and ribavirin therapy in children with hepatitis C remains uncertain. Ribavirin has yet to be evaluated adequately in children, and pediatric doses and safety have not been established. Thus, if children with hepatitis C are treated, monotherapy is recommended, and ribavirin should not be used outside of controlled clinical trials.

People with both HCV and HIV infection should be offered therapy for hepatitis C as long as there are no contraindications.

Indeed, hepatitis C tends to be more rapidly progressive in patients with HIV co-infection, and end-stage liver disease has become an increasingly common cause of death in HIV-positive persons. For these reasons, therapy for hepatitis C should be recommended even in HIV-infected patients with early and mild disease. Once HIV infection becomes advanced, complications of therapy are more difficult and response rates are less. The decision to treat people co-infected with HIV must take into consideration the concurrent medications and medical conditions. In particular, ribavirin may have significant interactions with anti-retroviral drugs used to treat HIV infection. In patients with co-infection, control of the HIV infection should be the first priority; in persons who are inadequately treated for HIV or who have low CD4 counts, therapy of concurrent HCV is unlikely to be successful and may have serious complications.

In many of these indefinite situations, the indications for therapy should be reassessed at regular intervals. In view of the rapid developments in hepatitis C today, better therapies may become available within the next few years, at which point expanded indications for therapy would be appropriate.

Patients with chronic hepatitis C should be advised on the likelihood of a beneficial outcome to antiviral therapy. For patients with genotypes 2 and 3, the likelihood of a sustained virological response is 70 to 80 percent. In patients with genotype 1, the likelihood of a sustained virological response is between 40 and 55 percent, but the individual likelihood correlates with several viral and patient factors. The major predictive factor for a response is the level

of HCV RNA in serum: response rates being higher if HCV RNA levels are lower—levels less than 800,000 IU/ml generally being considered low. Furthermore, response rates are higher in women than men, in younger than older persons, in persons with normal body weight compared with those who are overweight or obese, and in persons with lesser degrees of fibrosis on liver biopsy. Strikingly, response rates are also higher among Caucasian Americans and Asian Americans than among African American patients. Thus, average overall response rates in persons with HCV genotype 1 infection are 50 to 60 percent among Caucasian Americans, but only 25 to 30 percent among African American patients. The reasons for these racial differences are not known.

Patients with acute hepatitis C are a major challenge to management and therapy. Because such a high proportion of patients with acute infection develop chronic hepatitis C, prevention of chronicity has become a focus of attention. In small studies, 83 to 100 percent of persons treated within 1 to 4 months of onset have had resolution of the infection. What is unclear is when to initiate treatment, at what dose, for what duration, and with which regimen. A practical but rigorous approach is to start peginterferon (in usual doses) and ribavirin (800 mg daily) for 24 weeks if HCV RNA is still detected 3 months after onset of infection. The role of ribavirin and the use of shorter courses of therapy are currently under evaluation.

In patients with clinically significant extrahepatic manifestations, such as cryoglobulinemia and glomerulonephritis, therapy with interferon can result in remission of the clinical symptoms and signs. However, relapse after stopping therapy is common. In some patients, long-term or maintenance peginterferon therapy can be used despite persistence of HCV RNA in serum if clinical symptoms and signs resolve on therapy.

Who should not be treated?

Therapy is inadvisable outside of controlled trials for patients who have

- clinically decompensated cirrhosis because of hepatitis C

- kidney, liver, heart, or other solid-organ transplant

- specific contraindications to either monotherapy or combination therapy

Contraindications to peginterferon therapy include severe depression or other neuropsychiatric syndromes, active substance or alcohol abuse, autoimmune disease (such as rheumatoid arthritis, lupus erythematosus, or psoriasis) that is not well controlled, bone marrow compromise, and inability to practice birth control. Contraindications to ribavirin and thus combination therapy include marked anemia, renal dysfunction, and coronary artery or cerebrovascular disease, and inability to practice birth control.

Peginterferon has multiple neuropsychiatric effects. Prolonged therapy can cause marked irritability, anxiety, personality changes, depression, and even suicide or acute psychosis. Patients particularly susceptible to these side effects are those with pre-existing serious psychiatric conditions and patients with neurological disease.

Strict abstinence from alcohol is recommended during therapy of hepatitis C. Peginterferon therapy can be associated with relapse in people with a previous history of drug or alcohol abuse. Therefore, interferon should be given with caution to a patient who has only recently stopped alcohol or substance abuse. Typically, a 6-month abstinence is recommended before starting therapy, but this should be applied only to patients with a history of alcohol abuse, not to social drinkers. Patients with continuing alcohol or substance abuse problems should only be treated in collaboration with alcohol or substance abuse specialists or counselors. Patients can be successfully treated while on methadone or in an active substance abuse program. Indeed, the rigor and regular monitoring that accompany methadone treatment provide a structured format for combination therapy. The dose of methadone may need to be modified during peginterferon-based therapy for hepatitis.

Peginterferon therapy can induce autoantibodies, and a 24- to 48-week course triggers an autoimmune condition in about 2 percent of patients, particularly if they have an underlying susceptibility to autoimmunity (high titers of antinuclear or antithyroid antibodies, for instance). Exacerbation of a known autoimmune disease (such as rheumatoid arthritis or psoriasis) occurs commonly during peginterferon therapy.

Peginterferon has bone marrow suppressive effects. Therefore, patients with bone marrow compromise or cytopenias, such as a low platelet count ($< 75,000$ cells/mm^3) or neutropenia ($< 1,000$ cells/mm^3), should be treated cautiously and with frequent monitoring of cell counts. These side effects appear to be more common with peginterferon than standard interferon.

Ribavirin causes red cell hemolysis to a variable degree in almost all patients. Therefore, patients with a pre-existing hemolysis or anemia (hemoglobin < 11 grams [g] or hematocrit < 33 percent) should not receive ribavirin. Similarly, patients who have significant coronary or cerebral vascular disease should not receive ribavirin, as the anemia caused by treatment can trigger significant ischemia. Fatal myocardial infarctions and strokes have been reported during combination therapy with alpha interferon and ribavirin.

Growth factors such as erythropoietin to raise red blood cell counts or granulocyte stimulating factor to raise neutrophil counts have been used successfully to treat patients with cytopenias during combination therapy. The proper role, dose, and side effects of these adjunctive therapies have yet to be defined.

Ribavirin is excreted largely by the kidneys. Patients with renal disease can develop hemolysis that is severe and even life-threatening. Patients who have elevations in serum creatinine above 2.0 mg per deciliter (dL) should not be treated with ribavirin.

Finally, ribavirin causes birth defects in animal studies and should not be used in women or men who are not practicing adequate means of birth control. Peginterferon also should not be used in pregnant women, as it has direct antigrowth and antiproliferative effects.

Combination therapy should therefore be used with caution. Patients should be fully informed of the potential side effects before starting therapy.

A common question is whether liver biopsy is necessary before starting treatment of hepatitis C. The answer is that it is not necessary but is prudent and provides rationale for whether therapy is critical. Nevertheless, the major use of liver biopsy is to help in the decision of whether to initiate treatment or to delay until there are further advances in the field. In some situations, liver biopsy may not be very helpful. Patients with genotype 2 and 3, for instance, have a high rate of response and might be offered therapy regardless of the severity of hepatitis shown by liver biopsy. Furthermore, patients with genotype 1 who have laboratory or clinical evidence of advanced fibrosis can be assumed to have progressive liver disease, and therapy can be recommended without biopsy documentation. Finally, some patients wish to be treated regardless of severity of the underlying hepatitis and the liver biopsy results will not alter medical care. As response rates to therapy of hepatitis C improve, liver biopsy will play a lesser role in management.

Side Effects of Treatment

Common side effects of alpha interferon and peginterferon (occurring in more than 10 percent of patients) include

- fatigue

- muscle aches

- headaches

- nausea and vomiting

- skin irritation at the injection site

- low-grade fever

- weight loss

- irritability

- depression

- mild bone marrow suppression

- hair loss (reversible)

Most of these side effects are mild to moderate in severity and can be managed. They are worse during the first few weeks of treatment, especially with the first injection. Thereafter, side effects diminish. Acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen or naproxen may be helpful for the muscle aches and low-grade fever. Fatigue and depression are occasionally so troublesome that the dose of peginterferon should be decreased or therapy stopped early. Depression and personality changes can occur on peginterferon therapy and be quite subtle and not readily admitted by the patient. These side effects need careful monitoring. Patients with depression may benefit from antidepressant therapy using selective serotonin reuptake inhibitors. Generally, the psychiatric side effects resolve within 2 to 4 weeks of stopping combination therapy.

Ribavirin also causes side effects, and the combination is generally less well tolerated than peginterferon monotherapy. The most common side effects of ribavirin are

- anemia

- fatigue and irritability

- itching

- skin rash

- nasal stuffiness, sinusitis, and cough

Ribavirin causes a dose-related hemolysis of red cells; with combination therapy, hemoglobin usually decreases by 2 to 3 g/dL and the hematocrit by 5 to 10 percent. The amount of decrease in hemoglobin is highly variable. The decrease starts between weeks 1 and 4 of therapy and can be precipitous. Some patients develop symptoms of anemia, including fatigue, shortness of breath, palpitations, and headache.

The sudden drop in hemoglobin can precipitate angina pectoris in susceptible people, and fatalities from acute myocardial infarction and stroke have been reported in patients receiving combination therapy for hepatitis C. For these important reasons, ribavirin should not be used in patients with pre-existing anemia or with significant coronary or cerebral vascular disease. If such patients require therapy for hepatitis C, they should receive peginterferon monotherapy.

Ribavirin has also been found to cause itching and nasal stuffiness. These are histamine-like side effects; they occur in 10 to 20 percent of patients and are usually mild to moderate in severity. In some patients, however, sinusitis, recurrent bronchitis, or asthma-like symptoms become prominent. It is important that these symptoms be recognized as attributable to ribavirin, because dose modification (by 200 mg per day) or early discontinuation of treatment may be necessary.

Uncommon side effects of alpha interferon, peginterferon, and combination therapy (occurring in less than 2 percent of patients) include

- autoimmune disease (especially thyroid disease)

- severe bacterial infections

- marked thrombocytopenia

- marked neutropenia

- seizures

- depression and suicidal ideation or attempts

- retinopathy (microhemorrhages)

- hearing loss and tinnitus

Rare side effects include acute congestive heart failure, renal failure, vision loss, pulmonary fibrosis or pneumonitis, and sepsis. Deaths have been reported from acute myocardial infarction, stroke, suicide, and sepsis.

A unique but rare side effect is paradoxical worsening of the disease. This effect is assumed to be caused by induction of autoimmune hepatitis, but its cause is really unknown. Because of this possibility, aminotransferases should be monitored. If ALT levels rise to greater than twice the baseline values, therapy should be stopped and the patient monitored. Some patients with this complication have required corticosteroid therapy to control the hepatitis.

Options for Patients Who Do Not Respond to Treatment

Few options exist for patients who either do not respond to therapy or who respond and later relapse. Patients who relapse after a course of interferon or peginterferon monotherapy may respond to a course of peginterferon and ribavirin combination therapy, particularly if they became and remained HCV RNA negative during the period of monotherapy. The response rates and optimal dose (800 vs. 1,000 mg to 1,200 mg of ribavirin) and duration (24 or 48 weeks) of peginterferon and ribavirin for relapse or previous nonresponder patients have not been defined. The algorithm for treatment given above is for treatment of naive patients.

An experimental approach to treatment of nonresponders is the use of long-term or maintenance peginterferon, which is feasible only if the peginterferon is well tolerated and has a clear-cut effect on serum aminotransferase levels or liver histology, despite lack of clearance of HCV RNA. This approach is now under evaluation in long-term clinical trials in the United States. New medications and approaches to treatment are needed. Most promising for the future are the use of newer antivirals, such as RNA polymerase, helicase, or protease inhibitors.

Algorithm for Treatment

Make the diagnosis based on aminotransferase elevations, anti-HCV, and HCV RNA in serum.

↓

Assess for suitability of therapy and contraindications. Discuss side effects and the likelihood of a beneficial treatment outcome.

↓

Test for HCV genotype.

Consider doing a liver biopsy to assess the severity of the underlying hepatitis and need for current therapy.

↓

Genotype 1: Test for HCV RNA level immediately before starting therapy (baseline level).

↓

Genotype 1: Start therapy with peginterferon alfa-2a in a dose of 180 mcg weekly or peginterferon alfa-2b in a dose of 1.5 mcg per kg weekly in combination with oral ribavirin in two divided doses of 1,000 mg daily if body weight is < 75 kg (165 lbs) or 1,200 mg daily if > 75 kg.

↓

Genotype 2 or 3: Start therapy with peginterferon alfa-2a in a dose of 180 mcg weekly or with alfa-2b in a dose of 1.5 mcg per kg weekly and oral ribavirin 800 mg daily in two divided doses.

↓

All patients: At weeks 1, 2, and 4 and then at intervals of every 4 to 8 weeks thereafter, assess side effects, symptoms, blood counts, and aminotransferase levels.

↓

Genotype 1: At week 12, retest for HCV RNA level. If HCV RNA is negative or has decreased by at least two $\log_{10}$ units (such as from 2 million IU to 20,000 IU or from 500,000 IU to 5,000 IU or less), continue therapy for a full 48 weeks, monitoring symptoms, blood counts, and ALT at 4- to 8-week intervals. If HCV RNA has not fallen by two $\log_{10}$ units, stop therapy.

↓

Genotype 2 or 3: At 24 weeks, assess aminotransferase levels and HCV RNA and stop therapy.

↓

All patients: After therapy, assess aminotransferase levels at 2- to 6-month intervals. In responders, repeat HCV RNA testing 6 months after stopping.

Considerations: Before, During, and After Therapy

Before Starting Therapy

- Do a liver biopsy to confirm the diagnosis of HCV, assess the grade and stage of disease, and rule out other diagnoses. In situations where a liver biopsy is contraindicated, such as clotting disorders, combination therapy can be given without a pretreatment liver biopsy.

- Test for serum HCV RNA to document that viremia is present.

- Test for HCV genotype (or serotype) to help determine the duration of therapy and dose of ribavirin.

- Measure blood counts and aminotransferase levels to establish a baseline for these values.

- Counsel the patient about the relative risks and benefits of treatment. Side effects should be thoroughly discussed.

During Therapy

- Measure blood counts and aminotransferase levels at weeks 1, 2, and 4 and at 4- to 8-week intervals thereafter.

- Adjust the dose of ribavirin downward (by 200 mg at a time) if significant anemia occurs (hemoglobin less than 10 g/dL or hematocrit < 30 percent) and stop ribavirin if severe anemia occurs (hemoglobin < 8.5 g/dl or hematocrit < 26 percent).

- Adjust the dose of peginterferon downward if there are intolerable side effects such as severe fatigue, depression, or irritability or marked decreases in white blood cell counts (absolute neutrophil count below 500 cells/mm3) or platelet counts (decrease below 30,000 cells/mm3). When using peginterferon alfa-2a, the dose can be reduced from 180 to 135 and then to 90 mcg per week. When using peginterferon alfa-2b, the dose can be reduced from 1.5 to 1.0 and then to 0.5 mcg per kg per week.

- In patients with genotype 1, measure HCV RNA levels immediately before therapy and again (by the same method) at week 12. Therapy can be stopped early if HCV RNA levels have not decreased by at least two $\log_{10}$ units, as studies have shown that genotype 1 patients without this amount of decrease in HCV RNA are unlikely to have a sustained response (likelihood is < 1 percent). In situations where HCV RNA levels are not obtainable, repeat testing for HCV RNA by PCR (or TMA) should be done at 24 weeks and therapy stopped if HCV RNA is still present, as a sustained response is unlikely.

- Reinforce the need to practice strict birth control during therapy and for 6 months thereafter.

- Measure thyroid-stimulating hormone levels every 3 to 6 months during therapy.

- Patients with genotypes 2 or 3 can stop therapy at 24 weeks. Patients with genotype 1 who are HCV RNA negative at 24 weeks should continue therapy to a full 48 weeks.

- At the end of therapy, test HCV RNA by PCR to assess whether there is an end-of-treatment response.

After Therapy

- Measure aminotransferase levels every 2 months for 6 months.

- Six months after stopping therapy, test for HCV RNA by PCR (or TMA). If HCV RNA is still negative, the chance for a long-term "cure" is excellent; relapses have rarely been reported after this point.

Hope Through Research

Basic Research

A major focus of hepatitis C research has been to develop a tissue culture system that will enable researchers to study HCV outside the human body. This goal was achieved in part in 2005 when three different laboratories reported tissue culture systems using HCV, genotype 2. These systems are now being improved and used to study how the virus infects cells and whether spread can be blocked by antibodies and by different antiviral drugs. Animal models and molecular approaches to the study of HCV are also important. Understanding how the virus replicates and how it injures cells would be helpful in developing a means of controlling it and in screening for new drugs that would block it.

Diagnostic Tests

More sensitive and less expensive assays for measuring HCV RNA and antigens in the blood and liver are needed. Although current tests for anti-HCV are quite sensitive, a small percentage of patients with hepatitis C test negative for anti-HCV (false-negative reaction), and a percentage of patients who test positive are not infected (false-positive reaction). Also, there are patients who have resolved the infection but still test positive for anti-HCV. Convenient tests to measure HCV in serum and to detect HCV antigens in liver tissue would be helpful. Clinically, noninvasive tests such as ultrasound elastrography that would reliably predict liver fibrosis would be a very valuable advance.

New Treatments

Most critical for the future is the development of new antiviral agents for hepatitis C. Most interesting will be specific inhibitors of HCV-derived enzymes such as protease, helicase, and polymerase inhibitors. Drugs that inhibit other steps in HCV replication may also be helpful in treating this disease, by blocking production of HCV antigens from the RNA (IRES inhibitors), preventing the normal processing of HCV proteins (inhibitors of glycosylation), or blocking entry of HCV into cells (by blocking its receptors). In addition, nonspecific cytoprotective agents might be helpful for hepatitis C by blocking the cell injury caused by the virus infection. Further, molecular approaches to treating hepatitis C are worthy of investigation; these consist of using ribozymes, which are enzymes that break down specific viral RNA molecules, and antisense oligonucleotides, which are small complementary segments of DNA that bind to viral RNA and inhibit viral replication. The serious nature and the frequency of hepatitis C in the population make the search for new therapies of prime importance.

Prevention

At present, the only means of preventing new cases of hepatitis C are to screen the blood supply, encourage health professionals to take precautions when handling blood and body fluids, and inform people about high-risk behaviors. Programs to promote needle exchange offer some hope of decreasing the spread of hepatitis C among injection drug users. Furthermore, all drug users should receive instruction in safer injection techniques—simple interventions that can be life-saving. Vaccines and immunoglobulin products do not exist for hepatitis C, and development seems unlikely in the near future because these products would require antibodies to all the genotypes and variants of hepatitis C. Nevertheless, advances in immunology and innovative approaches to immunization make it likely that some form of vaccine for hepatitis C will eventually be developed.

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Patient Education Materials

The National Digestive Diseases Information Clearinghouse (NDDIC) has patient education materials on hepatitis C. To obtain free copies, contact the Clearinghouse at

NDDIC
2 Information Way
Bethesda, MD 20892–3570
Phone: 1–800–891–5389
Fax: 703–738–4929
Email: nddic@info.niddk.nih.gov
Internet: www.digestive.niddk.nih.gov

Patient education materials are also available from

American Liver Foundation
75 Maiden Lane, Suite 603
New York, NY 10038
Phone: 1–800–GO–LIVER (465–4837)
        1–888–4HEP–USA (443–7222)
        212–668–1000
Fax: 212–483–8179
Email: info@liverfoundation.org
Internet: www.liverfoundation.org

Centers for Disease Control and Prevention
1600 Clifton Road NE
Mail Stop G37
Atlanta, GA 30333
Phone: 404–371–5900
Fax: 404–371–5488
Internet: www.cdc.gov
Viral Hepatitis and Injection Drug Users
fact sheet available at
www.cdc.gov/idu/hepatitis/index.htm

Hepatitis Foundation International
504 Blick Drive
Silver Spring, MD 20904–2901
Phone: 1–800–891–0707 or 301–622–4200
Email: hepfi@hepfi.org
Internet: www.hepfi.org

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