

Chronic Hepatitis C: Current Disease Management

National Digestive Diseases Information Clearinghouse



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Introduction

The hepatitis C virus (HCV) is one of the most important causes of chronic liver disease in the United States. It accounts for about 20 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and 30 percent of cirrhosis, end-stage liver disease, and liver cancer. Almost 4 million Americans, or 1.8 percent of the U.S. population, have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. Hepatitis C causes an estimated 8,000 to 10,000 deaths annually in the United States.

A distinct and major characteristic of hepatitis C is its tendency to cause chronic liver disease. At least 75 percent of patients with acute hepatitis C ultimately develop chronic infection, and most of these patients have accompanying chronic liver disease.

Chronic hepatitis C varies greatly in its course and outcome. At one end of the spectrum are patients who have no signs or symptoms of liver disease and completely normal levels of serum liver enzymes. Liver biopsy usually shows some degree of chronic hepatitis, but the degree of injury 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, HCV RNA in serum, and elevated serum liver 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. About 20 percent of patients develop cirrhosis within 10 to 20 years of the onset of infection. Liver failure from chronic hepatitis C is one of the most common reasons for liver transplants in the United States. Hepatitis C might be the most common cause of primary liver cancer in the developed world. In Italy, Spain, and Japan, at least half of liver cancers could be related to HCV. Men, alcoholics, patients with cirrhosis, people over age 40, and those infected for 20 to 40 years are more likely to develop HCV-related liver cancer.

Researchers estimate that at least 20 percent of patients with chronic hepatitis C develop cirrhosis, a process that takes 10 to 20 years. After 20 to 40 years, a smaller percentage of patients with chronic disease develop liver cancer.

Risk Factors and Transmission

HCV is spread primarily by contact with blood and blood products. Blood transfusions and the use of shared, unsterilized, or poorly sterilized needles and syringes have been the main causes 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 disease. However, many patients acquire hepatitis C without any known exposure to blood or to drug use.

The major risk groups for hepatitis C are

- People who had blood transfusions before June 1992, when sensitive tests for anti-HCV were introduced for blood screening.
- People who have frequent exposure to blood products. These include patients with hemophilia, solid-organ transplants, chronic renal failure, or cancer requiring chemotherapy.
- Health care workers who suffer needle-stick accidents.
- Injection drug users, including those who used drugs briefly many years ago.
- Infants born to HCV-infected mothers.

Other groups who appear to be at slightly increased risk for hepatitis C are

- People with high-risk sexual behavior, multiple partners, and sexually transmitted diseases.
- People who use cocaine, particularly with intranasal administration, using shared equipment.

Maternal-Infant Transmission

Maternal-infant transmission is not common. In most studies, only 5 percent of infants born to infected women 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. Breast-feeding has not been linked to HCV's spread.

Sexual Transmission

Sexual transmission of hepatitis C between monogamous partners appears to be uncommon. Whether hepatitis C is spread by sexual contact has not been conclusively proven, and studies have been contradictory. Surveys of spouses and monogamous sexual partners of patients with hepatitis C show that less than 5 percent are infected with HCV, and many of these have other risk factors for this infection. For this reason, 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 and HIV.

Sporadic Transmission

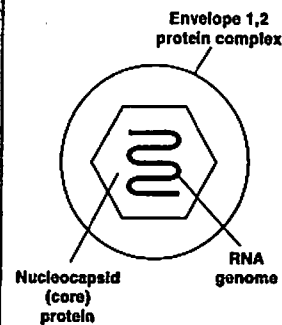
Sporadic transmission, when the source of infection is unknown, occurs in about 10 percent of acute hepatitis C cases and in 30 percent of chronic hepatitis C cases. These cases are also referred to as sporadic or community-acquired infections. These infections may have come from exposure to the virus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

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
- Nausea
- Poor appetite
- Muscle and joint pains.

HCV Viral Components



The Hepatitis C Virus

HCV is a small (40 to 60 nm in diameter), enveloped, single-stranded RNA virus of the family Flaviviridae. Because the virus mutates rapidly, changes in the envelope protein may help it evade the immune system. There are at least 6 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. 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 4 are more likely to respond to alpha interferon treatment.

Similarly, the physical exam is likely to be normal or show only mild hepatomegaly 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
- Ascites
- 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

Anti-HCV is detected by enzyme immunoassay (EIA). The third-generation test (EIA-3) used today is more sensitive and specific than previous ones. However, as with all enzyme immunoassays, 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 polymerase chain reaction (PCR) assay. 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 the physician first tests. 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 followup testing. In these situations, HCV RNA is usually present and confirms the diagnosis.

Recombinant Immunoblot Assay

Immunoblot assays are used to confirm anti-HCV reactivity, too. 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 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 without virus. 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 followup testing, including attempts to confirm the specificity by repeat testing for HCV RNA.

PCR Amplification

PCR 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 by PCR is particularly useful when aminotransferases 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. At present, however, there are no PCR assays approved by the Food and Drug Administration for general use, although commercial test systems are available. Many commercial laboratories offer their own PCR assays, which are not

subject to strict independent quality controls. Thus, the reliability and specificity of the PCR technique are not standardized. In addition, it is expensive and prone to technical or laboratory error. When ordering HCV RNA testing by PCR, the physician should use a high-quality laboratory willing to document standardization of the test.

Quantification of HCV RNA in Serum

Several methods are available for measuring the titer 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 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.

Viral load does not correlate with the severity of the hepatitis or with a poor prognosis (as it seems to in HIV infection); but viral load does correlate with the likelihood of a response to antiviral therapy. Rates of response to a course of alpha interferon 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 2 million copies per milliliter (mL).

In addition, monitoring viral load during the early phases of treatment may provide early information on the likelihood of a response. Yet because of the shortcomings of the current assays for HCV RNA level, these tests are not reliable guides to therapy. More sensitive and reliable methods of quantitating HCV RNA in serum are needed. Until that time, these tests should not be routinely used in practice.

Genotyping and Serotyping of HCV

There are 6 known genotypes and more than 50 subtypes of hepatitis C. The genotype of infection is helpful in defining the epidemiology of hepatitis C. 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 almost three times more likely to respond to therapy with alpha interferon or the combination of alpha interferon and ribavirin. Furthermore, when using combination therapy, the recommended duration of treatment depends on the genotype. For patients with genotypes 2 and 3, a 24-week course of combination treatment is adequate, whereas for patients with genotype 1, a 48-week course is recommended. For these reasons, testing for HCV genotype is often clinically helpful. Once the genotype is identified, *it need not be tested again*; genotypes do not change during the course of infection.

Normal Serum ALT Levels

Some 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

for patients who weigh less than 75 kilograms (165 pounds) or 1,200 mg for those who weigh more than 75 kilograms.

Treatment with interferon alone or combination therapy with interferon and ribavirin leads to rapid improvements in serum ALT levels in 50 to 75 percent of patients and the disappearance of detectable HCV RNA from the serum in 30 to 50 percent. However, a long-term improvement in liver disease usually occurs only if HCV RNA disappears during therapy and stays undetectable when therapy is stopped.

A response is considered to be “sustained” if HCV RNA remains undetectable for 6 months or more after therapy stops. With interferon monotherapy, 30 to 35 percent of patients become HCV RNA negative with treatment, but almost half of these relapse when treatment stops: The sustained response rate, therefore, averages only 15 to 20 percent. Combination therapy with interferon and ribavirin, however, leads to loss of HCV RNA on treatment in 50 to 55 percent of patients and a sustained loss in 35 to 45 percent. Thus, combination treatment results in both a higher rate of loss of HCV RNA on treatment and a lower rate of relapse when treatment is stopped.

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 interferon 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 (60 to 70 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 (25 to 35 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 using combination therapy.

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 alpha interferon 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.

Patients with cirrhosis found through liver biopsy can be offered therapy if they do not have signs of decompensation, such as ascites, persistent jaundice, wasting, variceal hemorrhage, or hepatic encephalopathy. However, interferon and combination therapy have not been shown to improve survival or the ultimate outcome in patients with preexisting cirrhosis.

Patients older than 60 years also should be managed on an individual basis, since the benefit of treatment in these patients has not been well documented and side effects appear to be worse in older patients.

The role of interferon 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.

In people with both HCV and HIV infection, benefits of therapy for hepatitis C have not been shown. The decision to treat people co-infected with HIV must also take into consideration the concurrent medications and medical conditions. If CD4 counts are normal or minimally abnormal ($> 400/\text{mL}$), responses are similar in frequency to those in patients who are not infected with HIV. The efficacy of combination therapy has not been documented in HIV-infected people, and ribavirin may have significant interactions with other antiretroviral drugs.

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.

In patients with clinically significant extrahepatic manifestations, such as cryoglobulinemia and glomerulonephritis, therapy with alpha interferon can result in remission of the clinical symptoms and signs. However, relapse after stopping therapy is common. In some patients, continual, long-term alpha interferon 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.
- Normal aminotransferase levels.

- A kidney, liver, heart, or other solid-organ transplant.
- Specific contraindications to either monotherapy or combination therapy.

Contraindications to alpha interferon 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, again, inability to practice birth control.

Alpha interferon 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 preexisting serious psychiatric conditions and patients with neurological disease. Interferon therapy is also associated with relapse in people with a previous history of drug or alcohol abuse. Alpha interferon should not be given to a patient who has only recently stopped alcohol or substance abuse. Typically a 2-year abstinence is recommended before starting therapy. Strict abstinence from alcohol is recommended during therapy with interferon.

Alpha interferon therapy can induce autoantibodies, and a 6- to 12-month 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 interferon therapy.

Alpha interferon has bone marrow suppressive effects. Therefore, patients with bone marrow compromise or cytopenias, such as low platelet count ($< 75,000$ cells/mm³) or neutropenia ($< 1,000$ cells/mm³) should be treated cautiously and with frequent monitoring of cell counts.

Ribavirin causes red cell hemolysis to a variable degree in almost all patients. Therefore, patients with a preexisting hemolysis or anemia (hemoglobin < 11 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.

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/dL should not be treated with ribavirin.

Finally, ribavirin causes birth defects in animal studies and should not be used in women who are not practicing adequate means of birth control. Alpha interferon 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.

Side Effects of Treatment

Common side effects of alpha interferon (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 may be helpful for the muscle aches and low-grade fever, and side effects may be less troublesome if interferon is taken in the evening. Fatigue and depression are occasionally so troublesome that the dose of interferon should be decreased or therapy stopped early. Depression and personality changes can occur on interferon therapy and be quite subtle and not readily admitted by the patient. These side effects need careful monitoring.

Ribavirin also causes side effects, and the combination is generally less well tolerated than interferon 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 pre-

Pegylated interferons are now being evaluated in prospective controlled trials. Other promising approaches are the use of other cytokines and the development of newer antivirals, such as RNA polymerase, helicase, or protease inhibitors.

The Future of Hepatitis C: Research

Basic Research

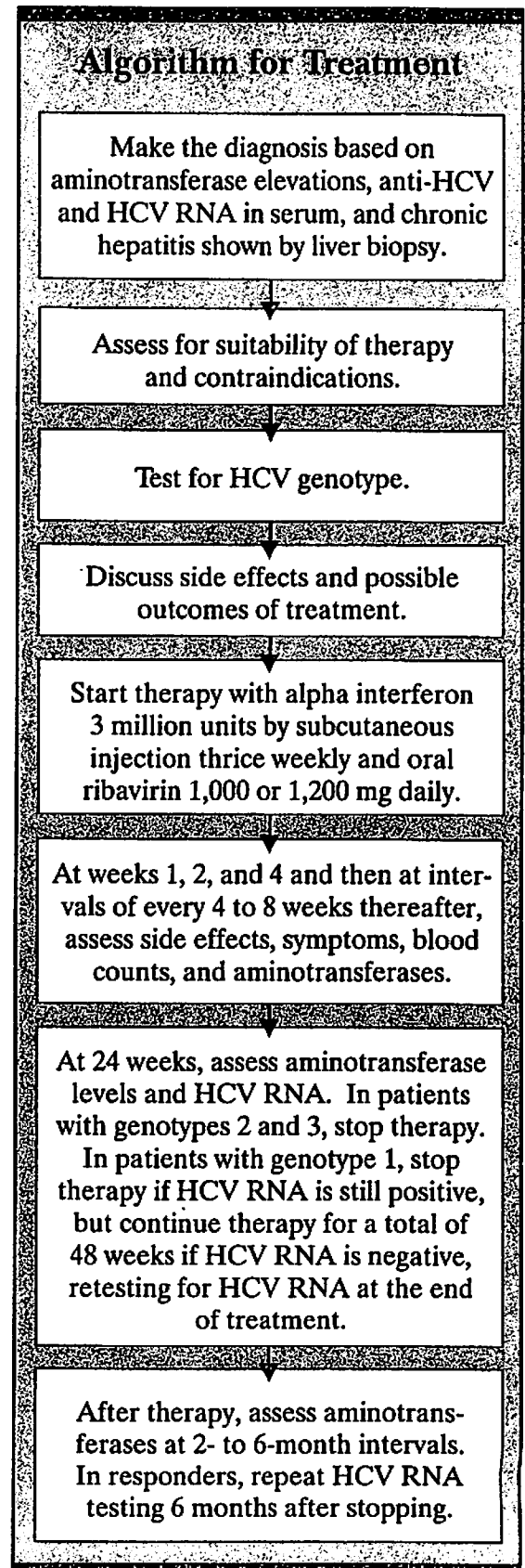
A major focus of hepatitis C research is developing a tissue culture system that will enable researchers to study HCV outside the human body. Animal models and molecular approaches to the study of HCV are also important. Understanding how the virus replicates and how it injures cells would be helpful in developing a means of controlling the virus 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.

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



Before Starting Therapy

- Do a liver biopsy to confirm the diagnosis of hepatitis C virus (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.
- Measure serum HCV RNA by polymerase chain reaction (PCR) to document that viremia is present.
- Test for HCV genotype (or serotype) to help determine the duration of therapy.
- Measure blood counts and aminotransferases 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 aminotransferases 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 \leq 30 percent) and stop ribavirin if severe anemia occurs (hemoglobin $<$ 8.5 g/dL or hematocrit $<$ 26 percent).
- Measure HCV RNA by PCR at 24 weeks. If HCV RNA is still present, stop therapy. If HCV RNA is negative and patient had genotype 1 (1a or 1b), continue therapy for another 24 weeks.
- 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.
- At the end of therapy, test HCV RNA by PCR to assess whether there is an end-of-treatment response.



After Therapy

- Measure aminotransferases every 2 months for 6 months.
- Six months after stopping therapy, test for HCV RNA by PCR. If HCV RNA is still negative, the chance for a long-term "cure" is excellent; relapses have rarely been reported after this point.

the normal processing of HCV proteins (inhibitors of glycosylation), or blocking entry of HCV into cells (by blocking its receptor). Nonspecific cytoprotective agents might also 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. All of these approaches remain experimental and have not been applied to humans. 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. 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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