INTRODUCTION

Hepatitis C virus (HCV) is the most common cause of chronic hepatitis in the United States. Millions of people are infected, the majority of whom are asymptomatic. Often people learn they have HCV infection after donating blood or when elevated transaminases are found during a routine physical examination. Diagnosis of HCV infection raises many questions for both the patient and physician, and the answers are often confusing and paradoxical. HCV is a very mild disease, yet it is one of the most common causes of cirrhosis and liver cancer and is the most common indication for liver transplantation. Patients with mild disease are unlikely to need treatment for HCV, yet they are the ones most likely to respond to treatment. HCV is rarely sexually or vertically transmitted, yet it can be transmitted via these pathways.

Since our last report on HCV in 1996 [1], public health initiatives and new treatment approaches have been introduced with the intent of improving management of this disease. In 1997, the National Institutes of Health (NIH) held a consensus conference to clarify the issues surrounding the care of persons with HCV. The NIH and American Red Cross have devised a look-back program to try to identify people who may have been exposed to tainted blood, and the Department of Veterans Affairs has made the identification and treatment of infected veterans a priority for care centers. Most importantly, the introduction of combination therapy using interferon and ribavirin has greatly improved response to treatment, and at long last we are starting to use the word “cured” to describe sustained responders who are HCV RNA–negative.

CASE STUDY

Initial Presentation

A 42-year-old woman reports to her primary care physician after she was found to have mildly elevated aspartate aminotransferase (AST) levels as part of a routine health examination.

Do these laboratory results warrant further investigation?

In the past, many physicians might not have investigated a mild elevation in transaminases in an asymptomatic individual. Those days are, hopefully, gone. Asymptomatic patients with HCV, hemochromatosis, and other liver diseases commonly present with mild transaminase elevations. This finding demands investigation as treatment may be required.

History and Physical Examination

Questioning reveals that the patient is an engineer for a commercial airline manufacturer. She drinks no more than 2 glasses of wine per day and denies any past or current problems with alcohol. She is married and has 3 children, all in good health. She has never had a blood transfusion but admits to using injection (IV) drugs a couple of times when she was a college sophomore. She has no symptoms but notes that she is easily fatigued. Her physical examination is completely normal.

Laboratory Evaluation

The physician orders a complete blood count and prothrombin time, a full liver panel, markers for viral hepatitis, and iron studies. Results are as follows:

- Hemoglobin 13.8 g/dL
- Hematocrit 41%
- Mean corpuscular volume 86 µm³
- Platelet count 287 × 10³/mm³
- Prothrombin time 11 seconds
- AST 62 U/L
- Alanine aminotransferase (ALT) 85 U/L
- Alkaline phosphatase 101 U/L
- Total bilirubin 0.7 mg/dL
- Hepatitis B surface antigen (HBsAg) negative
- Antibody to HBsAg (anti-HBs) negative

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Antibody to hepatitis B core antigen (anti-HBc) positive

Anti-HCV positive

Iron 62 µg/dL

Total iron-binding capacity 382 µg/dL

Ferritin 84 ng/mL

• What is the significance of these findings?

The patient has elevated aminotransferase levels, reflecting ongoing necrosis and inflammation of the liver. She is also anti-HCV-positive. As with HIV antibody, the presence of HCV antibody usually denotes ongoing HCV infection rather than immunity. In addition, the patient is anti-HBc-positive, which indicates that she has been exposed to HBV. We are not confident that she has eliminated the infection because she is anti-HBs-negative. This is a common finding among patients who have acquired HCV through IV drug use. For practical purposes, we do not consider these individuals to be infected with HBV, but recent studies using reverse transcriptase polymerase chain reaction assays (PCR) have found HBV virus in a large number of patients who are anti-HBc-positive and HBsAg/anti-HBs-negative [2].

• What is the epidemiology of HCV?

Epidemiology of HCV

After the identification of hepatitis B virus, blood transfusions were screened for HBsAg, and it was thought that the problem of transfusion-associated hepatitis would go away. It did not. Incidence of transfusion-associated hepatitis dropped, but to a new plateau of about 7% of persons receiving a series of transfusions or 1% per unit of blood transfused [3,4]. The NIH spent years trying to identify the infectious agent, which they knew to be a virus. They had an excellent animal model: the chimpanzee. The disease could be transmitted via infected human sera to chimps and from chimp to chimp. In 1989, after all standard immunologic and microscopic techniques failed, a private group led by Michael Houghton at Chiron Corporation (Emeryville, CA) identified the virus using molecular techniques to isolate a bit of viral RNA genome [5]. At the time, the disease was known as non-A, non-B hepatitis or transfusion-associated hepatitis. Affected persons had had blood transfusions and were generally older with underlying medical conditions. The fact that they had acquired a mild form of hepatitis was important but not a major concern given their other medical problems. We now understand that the majority of people with HCV acquired the infection when they were young, usually through IV drug use.

Estimates of the number of people infected with HCV in the United States range between 3 and 4 million [6]. Sixty-five percent of all HCV antibody–positive patients are between the ages of 30 and 49 years [7]. The majority are asymptomatic and come to the attention of their physician when a routine check of transaminases is found to be elevated, when applying for life insurance, or after trying to donate blood. The incidence of HCV infection probably peaked in the 1980s at 180,000 cases/year but has declined rapidly to the current level of 30,000 cases/year. The prevalence is higher in minority groups (2.1% of Hispanics, 3.2% of African Americans), and the highest prevalence is in African American males between the ages of 40 and 49 years, who have a prevalence rate of 9.8% [7]. It is estimated that 8000 to 10,000 people will die as a result of their infection each year, but this number is expected to triple as the many people who acquired the infection in their youth develop end-stage liver disease [8]. Chronic HCV infection is now the most common indication for liver transplantation and a major risk factor for hepatocellular carcinoma.

Since HCV was discovered by the identification of RNA genome, further work has revealed 6 different HCV genotypes. In the United States, about 85% of people are infected with HCV genotype 1a or 1b [9]. In parts of Europe, genotype 3 makes up a large percentage of infected patients. Some data suggest that genotype 1 is associated with a worse prognosis, but this is not clear.

• Are additional tests needed to confirm the diagnosis of HCV infection in this patient?

• What further evaluations are indicated at this time?

Tests for HCV Infection

The standard test for HCV infection is the third-generation enzyme immunoassay (EIA, ELISA), which detects antibodies against 3 or 4 different HCV antigens (Table 1). Because all of the antigens are in the same microtiter well, the test does not indicate which or how many serum antibodies are positive [10]. In the appropriate setting, this test has high specificity and high sensitivity. A more sophisticated assay for HCV antibody is the recombinant immunoassay (RIBA). In this assay, the same antigens used in the third-generation EIA are laid out separately so the reaction to individual antigens can be determined. The RIBA has traditionally been used as a confirmatory test after a positive EIA result, and many laboratories automatically use the RIBA when an EIA is found to be positive.
Newer assays, such as PCR, detect circulating HCV rather than the body’s response to the virus. Many think that these tests, which measure HCV RNA levels in the serum, are better confirmatory tests for HCV infection [11,12]. Clinically, the usefulness of these tests depends on the patient’s pretest probability of having the disease (Table 2). If a patient has elevated transaminases and a history of blood transfusions or IV drug use, then the sensitivity and specificity of the EIA is over 90% and a positive EIA almost certainly indicates chronic HCV infection; most hepatologists would confirm this finding with PCR for HCV RNA (Figure 1). If a patient with normal transaminases and no risk factors for infection is found to be anti-HCV-positive as part of a screening program, false-positive test results are common and the predictive value of a positive HCV RNA can be as low as 50% [10,11]. In such cases, RIBA can be a useful means of identifying false-positives, although many physicians would use PCR as the confirmatory test.

**Approach to Further Workup**

When evaluating the patient with HCV infection, it is important to take a detailed history that includes current and past alcohol consumption; medication use, including vitamin supplements and herbal remedies; and family history of liver disease. The physical examination should be directed toward signs of advanced liver disease such as splenomegaly, ascites, spider telangiectasias, peripheral edema, gynecomastia, jaundice, or fingernail changes. When results of standard blood tests are reviewed, the hematocrit, mean corpuscular volume, platelets, prothrombin time, bilirubin, and albumin should be examined for evidence of advanced liver disease.

Consideration should be given to ordering specific tests to evaluate for other possible liver diseases. In addition to iron studies, we would obtain antinuclear antibody (ANA) and antimitochondrial antibody (AMA) tests to exclude autoimmune hepatitis and primary biliary cirrhosis, screen for Wilson’s disease with a serum ceruloplasmin level. A hepatic ultrasound should be considered to ensure that there are no structural lesions in the liver such as hepatocellular carcinoma, adenoma, or giant hemangioma.
Figure 1. Algorithm for managing an asymptomatic patient who is seropositive for HCV antibody (anti-HCV-positive). ALT = alanine aminotransferase; HCV RNA PCR = polymerase chain reaction assay (confirmatory test for HCV); INF = interferon alfa.
Additional Testing

The physician states that based on initial test results and her past IV drug use, it is almost certain that the patient has chronic HCV infection. He explains that he would like to order some additional tests to confirm the diagnosis and evaluate for other liver diseases. The patient consents to the tests, adding that she is concerned that she may have infected her children or husband. She asks the physician for more information on precautions against spreading the infection.

- Is it likely that this patient transmitted the virus to her family members?

Transmission of HCV

Percutaneous exposure though IV drug use, blood transfusion, or accidental needle stick is by far the most common route of infection. Sexual or vertical transmission from mother to child can occur but is inefficient and probably not common. Mariam Alter at the Centers for Disease Control and Prevention (CDC) has extensively studied acute hepatitis in 5 counties in the United States, collecting epidemiologic data on risk factors for transmission. She found that about half of patients had IV drug use as a risk factor, the next largest group with the infection had no risk factors, and the next largest group after that had 3 or more sexual partners as a risk factor [6]. It must be kept in mind that these are epidemiologic data; that is, if patients admitted to having 3 or more sexual partners but not to IV drug use or another activity, their disease is considered to be sexually transmitted even though we do not have clear evidence that sexual activity is a common mode of transmission. For people with no risk factors (people who admitted to no high-risk behaviors), the mode of transmission is considered unknown.

In many cross-sectional studies of couples where 1 person is infected, the rate of infection in the sexual partner is low. In a Japanese study of people infected with HCV, no partners were infected among the group that had been married 10 years or less [13,14]. The problem in interpreting data on sexual transmission is that the studies are small cross-sectional or very short prospective studies, and investigators rely on history to determine the risk factors. Considering the data in aggregate, the NIH consensus panel concluded that sexual transmission can occur but at a low rate. According to the panel, people who are in a monogamous relationship do not need to change their sexual practices but should be aware of the increased risk; people who are not in a monogamous relationship should practice safer sex, including the use of latex condoms [15]. They also recommended testing for sexual partners of patients infected with HCV.

One group of investigators took a closer look at blood donors with no risk factors for HCV infection [16]. In this study, 42% of patients who initially denied drug use later admitted to using IV drugs and, interestingly, 68% admitted to using intranasal cocaine. The study suggests that the majority of HCV infection probably does occur via IV drug use and probably constitutes a larger percentage of patients than we suspect. It also indentified snorting cocaine as a possible mode of transmission. The mechanism is not clear but given the highly vascular nasal mucosa, it is suspected that passing a straw or other fomite from nose to nose may transfer infected blood.

Perinatal transmission from mother to child is a concern to many patients. It is well documented that HCV can be transmitted from mother to child, but as in sexual transmission, this occurs at a low rate, probably no more than 6% [17]. There is a higher rate of vertical transmission among those who are coinfected with HIV and patients with high levels of HCV RNA. Breastfeeding is not believed to transmit HCV and is considered safe. The NIH consensus panel recommended that children born to women with HCV be tested after 1 year (maternal HCV antibodies are present in most babies at birth) [15].

Given the percutaneous mode of transmission of HCV, the NIH consensus panel also recommended common-sense measures among household contacts, such as covering open wounds and not sharing toothbrushes or razor blades, but they did not think it necessary to avoid sharing meals or eating utensils. They also specifically stated that there was no evidence to support restricting HCV-infected children or adults from participating in social activities or employment.

Confirmation of HCV

The patient is found to be HCV RNA–positive with a viral count of 8 million copies/mL. HCV genotype is 1a. Her ANA and AMA tests are negative, and an ultrasound is normal. The patient is counseled about avoiding alcohol. She is puzzled that she has been infected with HCV for so long without knowing it. She has also heard that hepatitis C can cause cirrhosis and wants to know if she is going to die.

- What is the natural history of HCV?

Natural History of HCV

HCV is a very mild chronic inflammation of the liver, and most people are asymptomatic (Figure 2). The average person cannot recall symptoms of an acute viral hepatitis or jaundice. After exposure to HCV, RNA is detectable in serum in 1 to 3 weeks. Elevation in transaminases, indicating liver injury, occurs between 15 and 150 days after exposure. About 25% of infected people will develop symptoms of fatigue,
weakness, and anorexia. A smaller number may develop jaundice. While 15% of patients will clear the virus following acute HCV infection, 85% will not clear the virus and will develop chronic infection with persistent viremia. The majority of these will have elevated transaminases that can fluctuate greatly—between normal and 4 to 5 times the upper limit of normal. About one third will have persistently normal transaminases. There is 1 well-documented case report of fulminant hepatic failure and death from acute HCV infection, but this is a rare event [18]. The salient features of acute HCV are that it is a very mild infection and that it progresses to chronic HCV infection in most cases.

The natural history of chronic HCV infection is highly variable (Figure 3). In general, 20% or more of people with chronic hepatitis C will develop cirrhosis, and many of these will develop end-stage liver disease and die prematurely. However, most people will only have mild long-term inflammation and damage to their liver with some degree of fibrosis and will die of other causes. If we knew which people were going to develop cirrhosis and complications of liver disease and which people were not going to suffer ill effects from their infection, we could better care for our patients.

In a large cohort study from France, several factors have been linked to more serious liver disease with chronic HCV infection [19]. The first is alcohol; excess alcohol use has long been associated with a much higher percentage of those with HCV who are found to have cirrhosis on biopsy [20]. It appears that even moderate use of alcohol, even 2 drinks a day, is associated with more advanced liver disease on biopsy. Our current recommendation is that people stop drinking alcohol completely; it is the single best thing they can do for the health of their liver. Another factor that was associated with advanced liver disease is the number years the person had been infected with the virus. Other factors that have been associated with more advanced liver disease are male sex and becoming infected later in life.

- **What is the role of liver biopsy in providing prognostic information in HCV infection?**

**Role of Liver Biopsy**

Serum aminotransferase levels do not correlate with extent of liver damage in patients with chronic HCV infection. They are only a snap shot of what was going on in the liver on the day they were drawn. In patients with long-standing infection, mildly elevated liver enzymes may be associated with anything from near-normal liver histology to frank cirrhosis. To be informative, transaminases need to be measured frequently over a long period of time. Generally, a patient with very elevated transaminases daily for a prolonged period of time is likely to have more severe liver damage than a patient with normal or minimally elevated transaminases. However, a liver biopsy is necessary to determine the status of the liver.

Liver biopsy can assess current degree of inflammatory activity and, importantly, the degree of structural damage (ie, fibrosis). One particularly important finding on liver biopsy is bridging fibrosis. Here, the pathologist can identify scar tissue connecting portal triads or hepatic central veins (bridging of connective tissue from one portal area to another). Approximately 50% of patients with bridging fibrosis will develop cirrhosis in 5 to 10 years [21].

The decision to obtain a liver biopsy should be made together by the patient and the physician. To participate in decision making, patients must understand the purpose of the procedure and its attendant risks. Potential complications include bleeding (1 in 500 to 1000 biopsies) and, rarely, infection, hepatic hematoma, pneumothorax, and perforated gallbladder or other viscus. The purpose of liver biopsy is to provide information on extent of liver damage, which can aid the patient and physician in making treatment decisions. If the liver biopsy is normal, therapy would not be recommended. If bridging fibrosis is found, the physician should be more aggressive in recommending treatment. One question regarding HCV infection concerns people who have minimal liver damage on biopsy after 10 or 20 years of infection. It is...
unknown whether their liver disease will progress linearly (ie, their damage will double after another 10 to 20 years) or progress more rapidly in the later years. This uncertainty tempers our ability to counsel patients.

A unique group of patients with HCV infection are those with persistently normal transaminases. These patients tend to have mild liver disease and, interestingly, are less likely to respond to treatment. In this group, liver biopsy and treatment are not recommended [22]. Yet even this group of patients can have advanced liver disease, so if a patient requests liver biopsy despite physician recommendation, that request should be respected.

Referral to Hepatologist

The patient is referred to a hepatologist who reviews the role of liver biopsy in evaluating HCV infection. He explains that it is the best test to assess degree of liver damage and that the results may help him in counseling her about possible treatment; however, the decision is hers alone to make based on her attitudes about health and the weight she assigns to the competing risks and benefits of testing and treatment. The patient decides to undergo liver biopsy. During the procedure, the patient wonders if her arthritis could be related to HCV.

Several systemic illness are associated with HCV, including cryoglobulinemia, glomerulonephritis, and porphyria cutanea tarda [23,24]. More than 80% of patients with essential mixed cryoglobulinemia are positive for HCV antibody and HCV RNA. Deposition of immune complexes in small and medium-sized vessels can result in a vasculitic rash (palpable purpura), nondeforming arthritis, glomerulonephritis, Raynaud’s syndrome, and other somatic symptoms. Membranoproliferative glomerulonephritis with nephrotic range proteinuria and renal insufficiency is associated with HCV, usually with deposition of cryoglobulins identifiable on renal biopsy. HCV is strongly associated with porphyria cutanea tarda, especially in those with more advanced liver disease. Other diseases associated with HCV are lichen planus, corneal ulcers, autoimmune thyroiditis, non-Hodgkin’s lymphoma, and idiopathic pulmonary fibrosis [25].

Liver Biopsy Results

The patient’s biopsy shows moderate inflammation and bridging fibrosis.

- What is the predominant therapy for patients treated for HCV?
- What factors must be considered in deciding to recommend treatment?
Combination Therapy for HCV

In a discussion of treatment, it is helpful to provide a review of terms. Originally, responders were those who while on treatment normalized their ALT (biochemical responder). In current studies, we define a responder as a patient who becomes HCV RNA–negative (virologic responder) at the end of the treatment period (sometimes called the end-of-treatment response). If patients do not become HCV RNA–negative while on treatment, they are termed nonresponders. Patients who are responders are then tested 6 to 12 months after treatment has ended by PCR for HCV RNA. If they are still negative, they are termed sustained responders or long-term responders; if they are positive, they are termed relapers. Interferon was the first drug to receive FDA approval for the treatment of HCV. Initial studies had shown that about 40% of patients were responders, but after treatment was stopped, half of patients relapsed. Worse still, these initial data were from biochemical responders: transaminases had normalized, but the majority of patients did not get rid of the virus. Current data show that on interferon monotherapy, only about 10% of patients are sustained responders with loss of virus.

Much has changed in the past few years. The introduction of combination therapy with interferon and ribavirin in 1998 resulted in a significant increase in the number of people responding to treatment, and it has rapidly become the predominant form of treatment. Using standard-dose interferon 3 million units 3 times per week subcutaneously and oral ribavirin 1000 to 1200 mg per day for 48 weeks, about 40% of patients become long-term responders, a dramatic improvement over interferon alone. (Ribavirin by itself does not have a significant antiviral effect on HCV and is not effective against HCV). Several large, well-controlled studies in Europe and the United States found that overall, 38% to 43% of never-before-treated patients were sustained responders (ie, HCV RNA–negative 6 months after stopping treatment) [26,27]. Several factors had a significant effect on outcome (Table 3). In the United States, the majority of patients are genotype 1a or 1b; these patients did not respond as well, with about 28% to 31% having a sustained response. Those with genotype 1 who had a high viral load before treatment (>2 million copies/mL) did even more poorly. Patients with genotype 2 or 3 responded to treatment at a much higher rate, with 64% to 69% of patients having a sustained response. Additionally, this group only needs to be treated for 6 months. Other factors associated with a better response were little or no fibrosis, female gender, and age younger than 40 years [28]. About 20% of patients will need a dose reduction in medication while on treatment because of anemia or other adverse events. About 20% of patients will need to stop treatment because of adverse effects, the most common being depression.

### Table 3. Factors Associated With Response to Interferon/Ribavirin Treatment

<table>
<thead>
<tr>
<th>Increased response</th>
<th>Decreased response</th>
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<tr>
<td>Little or no fibrosis</td>
<td>Cirrhosis</td>
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<td>Low HCV levels</td>
<td>High HCV levels</td>
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<tr>
<td>HCV genotypes 2 and 3</td>
<td>HCV genotype 1</td>
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<tr>
<td>Age &lt; 40 yr</td>
<td>Age &gt; 40 yr</td>
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<td>Female gender</td>
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### Making Treatment Decisions

In making the decision to be treated, one must weigh the risks and benefits. If there was a simple, relatively inexpensive and effective cure for HCV, the decision to treat would be simple: we would treat everyone. However, treatment is complicated, prolonged, expensive, and has numerous side effects that make treatment an ordeal. On the other hand, about two thirds of patients with genotype 2 and 3 become long-term responders, and newer data indicate that about 95% of patients who are sustained responders 6 months after treatment will remain HCV RNA–negative years after treatment. While only about one third of genotype-1 patients will be sustained responders after treatment, when looked at from a broad perspective, even these results are impressive: There is no other example in modern medicine where we can eliminate a chronic viral infection one third of the time. Given that most people with HCV are asymptomatic and will not have their lives shortened by the disease, the decision to treat becomes complex. Ultimately, the decision to treat should be based on patient preferences in light of prognostic information; the considerable inconvenience, cost, and side effects of therapy; and the patient’s attitudes about health. The main contraindications to treatment are cirrhosis with evidence of hepatic decompensation and depression with suicidal ideation or past attempts at suicide. Patients both male and female must use acceptable forms of birth control because ribavirin is a teratogen.

There are no standard recommendations on the vaccination of patients with HCV infection. But since it is known that adults with chronic viral hepatitis are more susceptible to fulminant liver disease when infected with other hepatitis viruses, most hepatologists would recommend vaccinating patients against HBV and HAV [29,30]. As the patient is positive for anti-HBc, we would recommend that she receive only the HAV vaccine.
Treatment

The patient agrees to try combination therapy with interferon/ribavirin. In addition to providing instruction on self-injection and arranging for follow-up blood tests, her physician also provides information about local support groups and other resources for information about HCV (Table 4). Over the first week of treatment, the patient experiences significant fatigue, aches, and headaches with after-interferon injections. She decides to take the injections before bedtime, hoping to sleep through the worst of the side effects. She premedicates herself with acetaminophen and Benedryl prior to injection. At 4 weeks, her hemoglobin has dropped to 11.4 g/dL, her platelets have decreased to $115 \times 10^3$/mm$^3$, and her absolute neutrophil count is 1050. Her ALT is now normal. Since she is genotype 1a, it is planned to treat her for 1 year.

- What if the patient had not responded?

After 6 months of therapy, a qualitative HCV RNA will be obtained. If it is positive, she is a nonresponder and treatment should be stopped. If she is HCV RNA-negative, she should continue therapy for 6 more months. If the patient were to be a nonresponder or relapser after completion of combination therapy, we would recommend that she continue to avoid alcohol but would not have any further recommendations except to wait for a better treatment to become available. For the motivated patient or for those that are of particular concern, consideration can be given to high-dose interferon. Studies have been mixed, but in 1 large open-label study using consensus interferon (Infergen, Amgen Inc.) for relapsers, the sustained response was over 50%; for nonresponders, it was over 10% [31].

Future Directions

Many agents have been tried in the treatment of HCV infection; the most promising of these was amantadine. Initial reports suggested amantadine has a biochemical response of 60% and a virologic response of 27%; however, later controlled trials of amantadine were shown to have no sustained responders to treatment [32]. Studies are being done using amantadine as part of triple therapy with interferon and ribavirin to see if an even greater improvement in sustained responders can be obtained. Other compounds under study include nonsteroidal anti-inflammatory agents, ursodeoxycholic acid, thymosin alpha-1, IL-2 and IL-12.

An alternative delivery system for interferon is being developed by both Schering-Plough (PEG-Intron) and Hoffman-La Roche (Pegasys). Interferon bound to polyethylene glycol is injected once per week subcutaneously, resulting in constant delivery of interferon into the system. Initial reports using pegylated interferon alone showed a superior response against HCV than standard subcutaneous interferon. Studies are underway using pegylated interferon in combination with ribavirin.

Much work is being done to identify specific sites along the pathway of HCV uptake into hepatocytes, unpackaging, and viral replication that could be interrupted and thus prevent liver damage or, better yet, allow the immune system to eliminate the infection. With the success of combination therapy using nucleoside analogues and protease inhibitors against HIV, enzymes needed to replicate HCV such as protease, helicase, and replicase are being studied for potential inhibitors, but to date no candidate compounds have been found [33].

A vaccine for HCV is needed. The search for a vaccine so far has been frustrating because antibodies against HCV are not protective against infection [34]. The traditional method of isolating antigenic components of the virus and immunizing chimps have produced the expected humoral (antibody) response, but the induced antibodies have failed to prevent chimps from becoming infected. Other methods that can induce a cellular immune response are underway. These methods use either HCV peptides or actual HCV DNA to induce a class I MHC response and thus a more powerful T cell response rather than an antibody response [35].

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References

2. Cacciola I, Pollicino T, Squadrito G, Cerenza G, Orlando ME,


