Peginterferon and Ribavirin for Chronic Hepatitis C
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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

A 44-year-old woman with chronic hepatitis C has intermittent fatigue and persistent elevations in serum alanine aminotransferase levels. She has had hepatitis C for 10 years. The diagnosis was made after she attempted to donate blood and was found to have antibodies against the hepatitis C virus (HCV). On questioning, she reports having used illicit injection drugs in her early 20s.

The physical examination is normal except for obesity. The results of laboratory tests show an alanine aminotransferase level of 86 U per liter (normal value, <42); the alkaline phosphatase level, direct and total bilirubin levels, albumin level, prothrombin time, and complete blood count are normal. The serum HCV RNA level is 3.5 million IU per milliliter (genotype 1), and a liver biopsy specimen shows bridging fibrosis.

The patient is evaluated by a hepatologist, who recommends treatment with pegylated interferon and ribavirin.

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The Clinical Problem

Chronic hepatitis C is the major cause of chronic liver disease, cirrhosis, and liver cancer in most of the Western world, and it affects approximately 3.2 million Americans. The most common forms of HCV transmission, in descending order of frequency, are injection drug use, blood transfusion (before the advent of screening for the virus in the blood supply), and sexual exposure. After the discovery of HCV in 1989 and the availability of tests for antibodies against the virus in 1992, the rate of new cases of hepatitis C fell by more than 80%. Although acute cases are now uncommon, the burden of chronic HCV disease remains substantial because of the high rate of infection before discovery of the virus. As a consequence, the mortality rate associated with chronic disease is expected to double or triple in the next decade.

Hepatitis C is often clinically silent. Symptoms of jaundice develop in only one third of patients with acute infection, and most patients with chronic infection have few if any clinical manifestations, at least until cirrhosis is present. The natural history of hepatitis C is variable; cirrhosis eventuates in 20 to 30% of patients with chronic infection, generally after 2 to 3 decades. Once cirrhosis evolves, hepatocellular carcinoma develops in 1 to 4% of these patients per year.

Pathophysiology and Effect of Therapy

Hepatitis C is caused by a small, single-stranded RNA virus. The virus replicates in the liver at a high rate, resulting in average serum HCV RNA levels of 1 to 2 mil-
lion genome equivalents per milliliter. The six genotypes, or clades, of HCV vary in nucleotide sequence by 30 to 50%. The most common genotypes of HCV in the United States are genotype 1 (accounting for approximately 75% of cases), genotype 2 (approximately 15%), and genotype 3 (approximately 7%).

Although some patients with acute HCV infection have an immune response sufficient to clear the virus, chronic infection (defined as detectable HCV RNA for more than 6 months) develops in 55 to 85% of patients. Once established, chronic infection rarely resolves spontaneously. The hepatocellular injury seen in chronic HCV disease appears to be due not to a direct cytopathic effect of the virus but rather to immunologically mediated injury, with natural killer cells and CD8+ T cells playing a central role.

The currently recommended therapy for chronic hepatitis C is a combination of formulations of interferon alfa and ribavirin. Interferon alfa is a cytokine that has an important function in the innate antiviral immune response. It acts by attaching to cell-surface receptors that signal through the system of Janus-activated kinase and signal transducers and activators of transcription, leading to induction of multiple interferon-stimulated genes (Fig. 1). These genes include double-stranded RNases, inhibitors of viral protein translation, and proteins that destabilize viral messenger RNA. Interferon alfa also induces the expression of genes involved in the immune response, resulting in activation of natural killer cells, maturation of dendritic cells, proliferation of memory T cells, and prevention of T-cell apoptosis.

Ribavirin is an oral nucleoside analogue with broad activity against viral pathogens. Its mechanism of action against HCV is not completely clear. Ribavirin appears to have minimal direct activity against HCV replication, but it may lead to rapid and lethal mutation of virions or depletion of intracellular guanosine triphosphate, which is necessary for viral RNA synthesis. Ribavirin also has immune modulatory effects.

**Clinical Evidence**

Interferon alfa was approved as a therapy for hepatitis C in 1991. However, the overall rate of sustained virologic response, defined as the absence of HCV RNA in serum at least 6 months after the discontinuation of therapy, was low (generally <20%) with interferon alfa monotherapy. The subsequent addition of the oral antiviral agent ribavirin (Copegus, Roche; Rebetol, Schering-Plough; RibaspHERE, Three Rivers Pharmaceuticals) to interferon led to a marked improvement in rates of sustained virologic response (40 to 45%). Ribavirin alone lowered serum enzyme levels but had little effect on HCV RNA levels.

The most recent important advance in the treatment of hepatitis C was the development of a long-acting interferon, pegylated interferon (peginterferon), produced by the covalent attachment of polyethylene glycol to the interferon molecule. With its increased half-life, peginterferon can be given as a weekly dose. Two peginterferon formulations are currently approved for the treatment of hepatitis C: alfa-2a (Pegasys, Roche) and alfa-2b (Peg-Intron, Schering-Plough). In two large trials of these agents, the rates of sustained virologic response to a 48-week course of peginterferon and ribavirin were 54 and 56%, as compared with 44 and 47% with standard interferon and ribavirin and only 29% with peginterferon alone. Response rates were higher among patients with genotype 2 or 3 than among those with genotype 1. A subsequent trial of different regimens of peginterferon alfa-2a and ribavirin showed that patients with genotype 2 or 3 could be treated with a lower dose of ribavirin (800 mg rather than 1000 to 1200 mg daily) and that the rates of sustained virologic response after 24 weeks of therapy (81 and 84%) were similar to the rates after 48 weeks of therapy (79 and 80%).

**Clinical Use**

Therapy is recommended for adults with chronic hepatitis C who have detectable HCV RNA in serum, elevations in aminotransferase levels, histologic evidence of progressive liver disease, and no other serious coexisting conditions or contraindications. Specific qualitative assays for HCV RNA are available that have a lower limit of sensitivity of 10 to 50 IU (approximately 40 to 100 genome equivalents) per milliliter. In addition, HCV RNA can be quantified; most patients with chronic infection have HCV RNA levels between 0.2 and 5 million IU (approximately 1 to 20 million genome equivalents) per milliliter.
Interferon alfa engages receptors on the hepatocyte cell-surface membrane, causing them to dimerize and to activate Janus-activated and tyrosine kinases that phosphorylate the cytoplasmic signal transducers and activators of transcription (STAT) proteins. STAT1 and STAT2 dimerize and bind interferon regulatory factor 9 (IRF9), creating a large complex (interferon-stimulated gene factor 3, or ISGF3) that is translocated into the nucleus, where it binds to interferon-stimulated response elements (ISREs) on DNA. This engagement causes transcription of multiple (>100) interferon-stimulated gene (ISG) mRNAs, which exit the nucleus and encode proteins that alter cell metabolism and interfere with virus replication, protein synthesis, and assembly. Major ISGs thought to be important in inhibiting HCV replication include 2',5' oligoadenylate synthetase, which activates antiviral RNases; RNA-specific adenosine deaminase, which edits viral RNA; and protein kinase R, which inactivates protein translation from viral mRNA. The HCV replicative complex is associated with the cytoplasmic membranes of hepatocytes and comprises RNA replicative intermediates, viral mRNA, structural and nonstructural viral proteins, and assembling virions.
A liver biopsy is helpful in determining the severity of the inflammation and necrosis (the disease activity) and the stage of illness (the extent of permanent injury or fibrosis). In the two commonly used histologic scoring methods, the Metavir and Ishak Scoring systems, fibrosis is scored as none, portal fibrosis only, portal fibrosis with septa formation, bridging hepatic fibrosis, or cirrhosis. Therapy usually is recommended for patients with more than portal fibrosis only (an Ishak score ≥3 or a Metavir score ≥2). However, a liver biopsy has the major limitations of being costly, invasive, potentially harmful, and prone to sampling error. For these reasons, a liver biopsy cannot be considered to be a prerequisite for therapy. For patients with genotype 2 or 3 infection, rates of response to therapy are high, and a liver biopsy is not generally needed to make a decision regarding treatment. In patients with genotype 1 infection, a liver biopsy is helpful if there is little clinical evidence of advanced disease and if the patient is uncertain about whether to undergo treatment. For patients who want therapy regardless of the severity of the illness or for those with clinical evidence of fibrosis or progressive disease, therapy can be initiated without a liver biopsy.

Absolute contraindications to therapy with peginterferon and ribavirin include pregnancy, breast-feeding, and a known allergy to either drug. Relative contraindications because of the potential for side effects include decompensated liver disease (bilirubin level >1.5 mg per deciliter [25.6 μmol per liter]; prothrombin time >15 seconds or international normalized ratio ≥1.7; albumin level <3.4 g per deciliter; ascites; bleeding esophageal varices; or hepatic encephalopathy), major neuropsychiatric disease, coronary or cerebrovascular disease, renal failure, and a history of solid organ transplantation. Patients with active substance or alcohol abuse may also not be candidates for therapy, and those with recent substance abuse should receive counseling during treatment because of the risk of relapse. Patients with anemia, thrombocytopenia, or leukopenia should be treated with caution, because these abnormalities are worsened by treatment. In patients with renal dysfunction, the ribavirin must be adjusted, and such patients are at increased risk for ribavirin-induced hemolytic anemia.

Hepatitis C is more rapidly progressive in patients with human immunodeficiency virus (HIV) coinfection, particularly as the immunodeficiency worsens. Thus, it is appropriate to treat hepatitis C in all persons with HIV coinfection as early in the course of HIV infection as possible and regardless of the alanine aminotransferase level or the histologic features of the liver, as long as there are no other contraindications to treatment.

The currently recommended regimen for the treatment of chronic hepatitis C is the combination of weekly subcutaneous injections of peginterferon and twice daily oral doses of ribavirin (Table 1). The recommended dose of peginterferon alfa-2a is 180 μg per week and that of peginterferon alfa-2b is 1.5 μg per kilogram of body weight per week. The optimal duration of therapy and dose of ribavirin vary according to the HCV genotype. Patients with genotype 1 should receive ribavirin for 48 weeks at a daily dose of 1000 mg (if their body weight is 75 kg or less) or 1200 mg (if their weight exceeds 75 kg). Patients with genotype 2 or 3 infection should receive 24 weeks of combination therapy with a dose of 800 mg of ribavirin daily. There is little information on the treatment of hepatitis C in patients with genotypes 4, 5, and 6 and the regimen for genotype 1 is usually recommended for such patients.

The cost of a 48-week course of peginterferon and ribavirin ranges from $30,000 to $40,000, depending on local charges and the dose and brand of drugs used. The expenses for monitoring and physician visits also need to be considered in weighing the costs of therapy.

Three general patterns of response occur with therapy: a sustained virologic response, a transient virologic response and relapse or breakthrough, and nonresponse. In patients with a sustained virologic response, HCV RNA levels usually fall rapidly with the initiation of therapy, becoming undetectable within 4 to 24 weeks and remaining undetectable throughout the course of treatment and follow-up. Alanine aminotransferase levels have mild, nonprogressive hypertransaminasemia, and patients with normal alanine aminotransferase levels may also not be candidates for therapy, and those with recent substance abuse should receive counseling during follow-up.
Ferase levels fall within a few weeks after the decline in HCV RNA levels, usually become normal during treatment, and remain normal during follow-up. If a liver biopsy is performed, the histologic findings show marked improvement. With the use of current regimens, overall sustained virologic response rates are 75 to 80% among patients with HCV genotype 2 or 3 infection and 40 to 50% among those with genotype 1. Among patients with genotype 1, the rates of sustained virologic response are lower among blacks (28%) than among whites (52%). Other factors associated with a lower response rate are higher initial levels of HCV RNA (>600,000 IU per milliliter), male sex, higher body weight, and more advanced liver fibrosis.

Not all patients with HCV RNA that becomes undetectable during treatment have a sustained virologic response. In 10% of patients, HCV RNA reappears in serum later during the course of treatment (as a breakthrough), and in 20% it reappears when therapy is stopped (as a relapse). In patients with a relapse, HCV RNA usually reappears within a few weeks after the discontinuation of therapy, and alanine aminotransferase levels rise toward pretreatment levels thereafter. Relapses are more common with shorter courses than with longer ones, with interferon monotherapy than with combination therapy, and with a delayed loss of HCV RNA during treatment.

In some patients with chronic hepatitis C, HCV RNA remains detectable during treatment, although the level may decline. In these persons, alanine aminotransferase levels usually remain elevated, and treatment provides little clinical benefit. Nonresponse is uncommon among patients with genotype 2 or 3, but occurs in at least 30% of patients with genotype 1.

### Table 1. Therapy for Chronic Hepatitis C.

<table>
<thead>
<tr>
<th>Genotype*</th>
<th>Dose of Peginterferon</th>
<th>Dose of Ribavirin</th>
<th>Duration (wk)</th>
<th>Reason for Early Discontinuation of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peginterferon alfa-2a, 180 μg weekly, or alfa-2b, 1.5 μg/kg weekly</td>
<td>1000 mg or 1200 mg daily, according to body weight (≤75 kg or &gt;75 kg)</td>
<td>48</td>
<td>Nonresponse: discontinue at 12 wk if &lt;2 log_{10} IU/ml decline in HCV RNA levels or at 24 wk if HCV RNA is still detectable</td>
</tr>
<tr>
<td>2 or 3</td>
<td>Peginterferon alfa-2a or alfa-2b (same doses as above)</td>
<td>800 mg daily</td>
<td>24</td>
<td>Nonresponse: unusual Rapid response: discontinue at wk 12–16 if HCV RNA undetectable by week 4</td>
</tr>
</tbody>
</table>

* Genotype 4, 5, or 6 infection should be treated with the regimen recommended for genotype 1 infection.

#### Adverse Effects

Side effects of peginterferon and ribavirin affect virtually all patients who receive treatment (Table 2). The most common adverse effects of peginterferon are muscle aches and fatigue, but more difficult to manage are the psychological side effects such as depression, anxiety, irritability, sleep disturbance, and difficulty concentrating. These side effects typically are managed with counseling, antidepressant drugs, or anxiolytic agents, with variable success. The most common side effect of ribavirin is hemolysis, and anemia is the major reason for dose reduction. The stress of the sudden onset of anemia can induce myocardial infarction in persons with preexisting coronary artery disease or stroke in those with cerebrovascular disease. Ribavirin is also teratogenic, and strict adherence to an effective means of birth control is mandatory for both women and men who receive this drug. Serious side effects of combination therapy occur in 1 to 2% of patients, and permanent injury and death can occur.

Before treatment, patients should be fully informed of the potential side effects, and arrangements should be made for monitoring of symptoms and blood counts, with visits at least monthly during treatment. Among patients who receive treatment for 48 weeks, dose reductions (usually of ribavirin) are necessary in 30 to 40% of patients and early discontinuation is necessary in up to
Ribavirin should be reduced in increments of 200 mg daily and can be temporarily withheld in the event of severe anemia. The dose of peginterferon alfa-2a can be reduced from 180 to 135 μg per week, and the dose of alfa-2b can be reduced from 1.5 to 1.0 μg per kilogram per week. Further reductions in the dose of peginterferon are associated with reductions in rates of sustained virologic response.

Areas of Uncertainty

Peginterferon is not yet approved for use in children, although prospective controlled trials are under way. Pilot studies suggest that the rate of response to combination therapy in children is similar to that in adults and that children may have better tolerance of both interferon and ribavirin.

Although neither standard nor pegylated interferons are approved for the treatment of acute hepatitis C, several prospective studies have shown excellent responses when therapy is started within 6 months after the onset of infection, with rates of sustained virologic response of 85% or greater. Left untreated, acute hepatitis C progresses to chronic hepatitis in up to 75% of adults. Unfortunately, treatment of acute hepatitis C is associated with high rates of side effects. The optimal doses have yet to be defined, but a 24-week course of peginterferon at standard doses and ribavirin at a dose of 800 mg daily is more than adequate.

Improved regimens or formulations of peginterferon and ribavirin are needed to prevent or control disabling side effects and reduce costs. One practical approach is the use of abbreviated courses of treatment. Therapy can be discontinued early if there is no virologic response, making further therapy futile, or if there is a rapid virologic response, making prolonged therapy unnecessary.

Thus, further therapy is probably futile after 24 weeks in patients with genotype 1 who remain HCV RNA–positive, since they are unlikely to have a sustained response. Furthermore, if the level of HCV RNA does not decrease by more than 2 log10 IU per milliliter or does not become undetectable after 12 weeks of treatment, nonresponse can be predicted in 98 to 100% of instances, and therapy can be discontinued.

Therapy can also be curtailed if there is a rapid response. Several recent studies have shown that treatment can be abbreviated in patients who become HCV RNA–negative within 4 weeks of starting therapy. Among such patients, therapy can be discontinued at 12 to 16 weeks in those with genotype 2 or 3 and at 24 weeks in those with genotype 1 and low baseline levels of HCV RNA.

Guidelines

Current indications for the treatment of hepatitis C are based on statements from a Consensus Development Conference Panel of the National Institutes of Health, which are supported by treatment guidelines published by two academic societies. Persons with chronic hepatitis C who are 18 years of age or older, are willing to be treated, and do not have contraindications to treatment are candidates for therapy if they have detectable HCV RNA in serum and evidence of chronic hepatitis (either elevated serum alanine aminotransferase levels or the presence of considerable necroinflammatory activity and fibrosis on liver biopsy). A step-by-step description of the management of hepatitis C is provided at http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc/index.htm.
RECOMMENDATIONS

The patient described in the vignette is an appropriate candidate for combination therapy with peginterferon and ribavirin on the basis of findings of HCV RNA in serum, elevated alanine aminotransferase levels, and a liver biopsy specimen showing bridging fibrosis. The only alternative is observation without therapy, in the hope that more potent agents will become available within the next 3 to 5 years. The potential for chronic hepatitis C to progress in the interim, however, provides support for the initiation of therapy now. The presence of genotype 1 calls for a 48-week course of therapy with weekly injections of either peginterferon alfa-2a (180 μg) or alfa-2b (1.5 μg per kilogram) and 1200 mg of oral ribavirin daily. The patient’s symptoms should be monitored and blood counts obtained regularly, with dose adjustments as necessary. Factors that are predictive of a successful response include female sex and the absence of coexisting conditions; those predictive of a poor response include obesity and a high baseline level of HCV RNA.

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REFERENCES


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