REVIEW

Treatment of hepatitis C

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ABSTRACT: Hepatitis C virus is a leading cause of chronic liver disease, with over 170 million people infected worldwide. It is also the leading indication for liver transplantation. Complications from chronic hepatitis C infection include cirrhosis, hepatic decompensation, and hepatocellular carcinoma. As a result, treatment strategies to prevent such complications have been widely researched, although many questions remain unanswered. To date, the standard therapy for chronic hepatitis C infection is the combination of peginterferon and ribavirin. Treatment strategies differ based on factors such as genotype and liver biopsy results. Other strategies must be considered for special groups, such as patients with acute hepatitis C infection, hepatitis C/human immunodeficiency virus (HIV) coinfection, and prior nonresponse to interferon or relapse after its use. The goal of therapy is to achieve a sustained virologic response (ie, no detectable hepatitis C ribonucleic acid 6 months after completion of therapy). The substantial adverse effects associated with both interferon alfa and ribavirin often make it difficult for patients to continue with their therapies.

Background

Hepatitis C is a leading cause of chronic liver disease1,2 and is currently the most common indication for liver transplantation in the United States.3 Over 4 million people have been exposed to hepatitis C in the United States and over 170 million people have been exposed worldwide.4

Hepatitis C is transmitted through contact with blood and blood products. The leading risk factor for hepatitis C infection today is injection drug use (Table 1).5-7 Other potential modes of transmission, although less common, include occupational exposure, sexual transmission, intranasal cocaine use, tattooing, body piercing, and maternal-infant spread.8-12 Recipients of therapeutic blood products before 1992, when screening became possible with the availability of serological markers, are also considered to be at risk of chronic hepatitis C infection.13 Patients with known risk factors should be screened for hepatitis C using an enzyme immunoassay (Figure 1).14 Positive enzyme immunoassay test results should be confirmed with either a recombinant immunoblot assay or hepatitis C ribonucleic acid (RNA) measurement.15 Hepatitis C RNA measurement, which is considered the “gold standard” for the diagnosis of hepatitis C, has the advantage over the recombinant immunoblot assay of not only confirming an exposure to hepatitis C but also determining ongoing viral replication. Patients with a positive enzyme immunoassay but a negative hepatitis C RNA assay may have cleared the infection, may have hepatitis C RNA that is below the level of detection, or may never have been exposed to hepatitis C (false positive). A recombinant immunoblot assay would confirm that the enzyme immunoassay is a true positive. Referral to a hepatologist for counseling, education, and treatment consideration should be considered for any patient who is found to have hepatitis C.

The incubation period of hepatitis C is approximately 7 weeks.16 Hepatitis C is an uncommon cause of acute hep-
atitis in the United States. Hepatitis A is responsible for 40% to 55% of acute hepatitis, and hepatitis B is responsible for another 30% to 35%; hepatitis C accounts for only 12% to 16% of acute infections.\(^6\) Chronic hepatitis C is difficult to assess, because it is frequently subclinical, so many patients are not even aware that they are infected. Patients with chronic hepatitis C are at risk of cirrhosis and hepatocellular carcinoma.\(^17\)

There are 6 genotypes and numerous subtypes of hepatitis C based on RNA sequence diversity of the genome. Genotypes 1 and 2 are found worldwide, genotype 3 mostly in South and Southeast Asia, genotype 4 predominantly in Africa and the Middle East, genotype 5 mostly in South Africa, and genotype 6 mainly in Hong Kong and Vietnam. In the United States, genotype 1 accounts for more than 70% of all infections.\(^4\) Genotype should be assessed in patients who are being considered for treatment. The genotype predicts the likelihood of achieving a sustained virologic response and determines how long treatment should be continued.\(^18\)\textasciitilde25\)

Table 1  Risk factors for hepatitis C infection

<table>
<thead>
<tr>
<th>Injection drug use</th>
<th>Recipient of clotting factor before 1987</th>
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<tbody>
<tr>
<td></td>
<td>Intranasal cocaine use</td>
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<td></td>
<td>Sex with multiple partners</td>
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<tr>
<td></td>
<td>Body piercing</td>
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<tr>
<td></td>
<td>Long-term hemodialysis</td>
</tr>
<tr>
<td></td>
<td>Occupational exposure (eg, needle stick)</td>
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<tr>
<td></td>
<td>Perinatal transmission</td>
</tr>
<tr>
<td></td>
<td>Blood transfusion or organ transplantation before 1992</td>
</tr>
</tbody>
</table>

Adapted from Centers for Disease Control and Prevention.\(^13\)

Liver biopsy

A liver biopsy is recommended to assess the severity of liver disease and the need for antiviral therapy. Liver biopsy is optional in patients with genotype 2 and 3 due to the high likelihood of viral response.\(^26\),\(^27\)

Repeat biopsies can also be useful to evaluate the progression of the disease in patients who have opted against treatment or in patients who did not respond to their initial therapy and are considering another course of therapy. Regardless of the alanine aminotransferase levels, liver biopsy should be performed when the results will influence whether treatment is recommended.\(^27\) Advanced fibrosis that requires antiviral therapy is seen in up to 40% of patients with persistently normal alanine aminotransferase levels.\(^28\) The major limitations of liver biopsy are its sampling variability and the risk of adverse events.\(^29\)\textasciitilde31\ In one study, the incidence of severe adverse events in 98 445 liver biopsies was 0.3 percent, with a mortality rate of 0.03 percent.\(^32\)

Treatment goals

The objective of therapy is to eradicate the virus and prevent potential complications from chronic hepatitis C infection. The risk of chronic disease in infected patients is greater than 80%.\(^33\)\textasciitilde37\ Among patients who develop chronic infection, 5% to 20% might develop cirrhosis, generally over the course of 20 to 30 years \(^38\)\textasciitilde41; among these cirrhotic patients, there is a 30% risk of developing decompensated liver disease after a decade, and a 1% to 2% yearly risk of developing hepatocellular carcinoma.\(^42\) Extrahepatic manifestations, such as cryoglobulinemia, that may lead to additional morbidity, and mortality must also be considered.\(^43\)

Efficacy of the treatment is assessed by measurements of hepatitis C RNA viral load (Table 2). The goal is to achieve a sustained virologic response, defined by the continued absence of hepatitis C RNA 6 months after the completion of treatment. The likelihood of achieving a sustained virologic response can be predicted at 3 months (Figure 2). If
the hepatitis C RNA does not drop by at least 2 logs at 3 months after initiating therapy, treatment should be discontinued, because the likelihood of a sustained virologic response is only 0% to 3%.24,25; these patients are termed nonresponders, in whom treatment strategies may need to be reconsidered (see below). Ongoing studies are assessing whether the early virologic response could be less than 12 weeks. Relapsers are patients who had undetectable hepatitis C RNA levels during therapy but levels that became detectable when therapy was discontinued.

**Antiviral treatment**

All patients with chronic hepatitis C infection should be considered potential candidates for therapy.39 In the absence of contraindications (Table 3), treatment is recommended for patients who are at increased risk of developing cirrhosis, generally defined by a measurable hepatitis C RNA level and liver biopsy showing portal or bridging fibrosis along with at least moderate inflammation and necrosis.

The past decade has seen a steady improvement in therapies against hepatitis C. In the mid-1990s, monotherapy with interferon glycoproteins with antiviral and immunomodulatory activity,44 administered by an injection 3 times weekly for 6 to 12 months, was associated with an overall sustained virologic response of 6% to 10%.45-47 The addition of ribavirin (a guanosine nucleoside analog that is able to inhibit the replication of viruses) to interferon in the late 1990s was associated with an increase in sustained virologic response to approximately 30%.18,19,48 Of note, ribavirin monotherapy does not have any appreciable effect on hepatitis C RNA levels.49 Realizing the importance of sustained interferon levels, the interferon product was pegylated, a process by which polyethylene glycol is covalently attached to a protein to increase its half-life, thereby resulting in better response rates (Table 4). Currently, the standard of care for the treatment of hepatitis C is the combination of peginterferon and ribavirin (Table 5), with a monthly cost of

![Figure 2](image)

**Figure 2** Use of early virologic response to predict sustained virological response. Data from Manns et al24 and Fried et al.25 *Probability of achieving a sustained virologic response.

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**Table 3** Absolute contraindications to hepatitis C therapy

<table>
<thead>
<tr>
<th>Contraindication</th>
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<tbody>
<tr>
<td>Active psychiatric illnesses, such as major depression, schizophrenia, or bipolar disorder that is not controlled</td>
</tr>
<tr>
<td>Having undergone renal, heart, or lung transplant</td>
</tr>
<tr>
<td>Comorbid conditions known to be exacerbated by interferon and ribavirin therapy, such as autoimmune hepatitis</td>
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<tr>
<td>Untreated hyperthyroidism</td>
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<tr>
<td>Severe concurrent disease such as severe hypertension, heart failure, considerable coronary artery disease, poorly controlled diabetes mellitus, severe chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Known hypersensitivity to drugs used to treat hepatitis C</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Breast feeding</td>
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<tr>
<td>Inability to practice birth control</td>
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</tbody>
</table>

*Data adapted from National Institutes of Health26 and Strader et al.27*

**Table 4** Likelihood of sustained virologic response in different patient population settings

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reference</th>
<th>Sustained virologic response (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis C</td>
<td>50-51,53</td>
<td>80-100 (overall with early intervention)</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>24,25,54</td>
<td>Genotype 1: 42-65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genotypes 2 and 3: 76-88</td>
</tr>
<tr>
<td>Subsets of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonresponders/relapsers†</td>
<td>59</td>
<td>18 (overall)</td>
</tr>
<tr>
<td>HIV/hepatitis C coinfection‡</td>
<td>65,66,67</td>
<td>Genotype 1: 17-29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genotypes 2 and 3: 44-73</td>
</tr>
<tr>
<td>Liver transplant recipients</td>
<td>79-81</td>
<td>26-45 (overall)</td>
</tr>
</tbody>
</table>

*Treatment using peginterferon and ribavirin in all settings, except in acute hepatitis C, in which interferon was used with or without ribavirin.†Patients who did not respond to interferon or to interferon plus ribavirin or who relapsed after these treatments.‡In one study, the response rates in patients with genotype 1 and 4 were analyzed together, as were the response rates of genotype 2, 3 and 5.47
approximately $1200 for peginterferon and $1100 for ribavirin.

The most common adverse effects associated with interferon include fatigue and flu-like symptoms (Table 6); interferon can also cause neutropenia and thrombocytopenia. With ribavirin, dose-dependent and reversible hemolytic anemia is the most prominent adverse effect, whereas the most serious potential adverse effect is teratogenicity. Two forms of contraception must be used during therapy and for 6 months following treatment cessation.

The decision of whether to continue antiviral treatment depends on the severity of adverse effects, their effect on quality of life, and the degree of underlying histologic damage. Peginterferon and ribavirin should be discontinued if the hemoglobin level is less than 8.5 g/dL, the white blood cell count is less than $1 \times 10^9/L$, the absolute neutrophil count is less than $0.5 \times 10^9/L$, and/or platelet count is less than $50 \times 10^9/L$.

### Treatment

#### Acute hepatitis C

Most patients with acute hepatitis C are asymptomatic, thus making it difficult to identify those with de novo infection. Hepatitis C RNA is detectable as early as 1 to 2 weeks following exposure, and aminotransferase levels start to rise after 6 to 12 weeks, and hepatitis C antibodies are detected as early as 8 weeks after exposure. Spontaneous viral clearance may occur during the first 12 weeks after infection.

Due to the difficulty of identifying acute hepatitis C infection, only 1 randomized, prospective trial has assessed the treatment of acute disease. Various studies demonstrate excellent sustained virologic responses with earlier treatment. Interestingly, over 50% of patients who present with symptomatic acute hepatitis C clear the virus spontaneously. In the only controlled study of acute hepatitis C, patients were randomized to interferon monotherapy starting 8 weeks (early intervention) or 1 year (late intervention) after infection. The sustained virologic response was 100% with early intervention but only 53% with late intervention.

These aggregate data suggest that the sustained virologic response is higher when treatment is instituted no more than 3 months after infection, although it may be prudent to wait 12 weeks to allow for spontaneous resolution. Although the optimal dose and duration of treatment of acute hepatitis C is unclear, patients may benefit from 6 months of interferon therapy. Other options include peginterferon, with and without ribavirin.

Currently, the best treatment for acute hepatitis C is a 6-month course of peginterferon and ribavirin (doses in Table 5). Although most studies used interferon in the treatment of acute hepatitis C, peginterferon is more convenient to use. Moreover, the addition of ribavirin to peginterferon is associated with a greater probability of a virologic response without a concomitant exacerbation of adverse effects.

### Chronic hepatitis C

#### Elevated aminotransferase levels

Several studies have compared the safety and efficacy of peginterferon and ribavirin with standard interferon and ribavirin for the treatment of chronic hepatitis C in patients with elevated aminotransferase levels. In these studies, peginterferon and ribavirin were more efficacious without having more adverse effects. With peginterferon and ribavirin, the overall sustained virologic response is between 54% and 63%, compared with a rate between 44% and 46% with interferon and ribavirin. Predictors of poor sustained virologic response include geno-

#### Table 5 Doses of peginterferon and ribavirin

<table>
<thead>
<tr>
<th>Peginterferon type and dose</th>
<th>Ribavirin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a 180 mg/wk</td>
<td></td>
</tr>
<tr>
<td>Genotype 1</td>
<td>1000 mg/d if weight ≤75 kg</td>
</tr>
<tr>
<td>Genotype 2 and 3</td>
<td>1200 mg/d if weight &gt;75 kg</td>
</tr>
<tr>
<td>Peginterferon alfa-2b 1.5 mg/kg/wk</td>
<td>800 mg/d</td>
</tr>
</tbody>
</table>

*Food and Drug Administration approved doses. However, weight-based ribavirin is commonly used in clinical practice with peginterferon alfa-2b.
†Peginterferon is administered subcutaneously and ribavirin is administered orally in divided doses twice daily.

#### Table 6 Selected common adverse effects reported with interferon and ribavirin

<table>
<thead>
<tr>
<th>Clinical adverse effect</th>
<th>Interferon and ribavirin (%)</th>
<th>Peginterferon and ribavirin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>55-60</td>
<td>47-64</td>
</tr>
<tr>
<td>Fever</td>
<td>33-56</td>
<td>39-46</td>
</tr>
<tr>
<td>Headache</td>
<td>52-58</td>
<td>47-62</td>
</tr>
<tr>
<td>Myalgia</td>
<td>50</td>
<td>42-56</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>28</td>
<td>24-34</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>29-43</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>15-17</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>24</td>
<td>23-26</td>
</tr>
<tr>
<td>Alopecia</td>
<td>32-34</td>
<td>21-36</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>36</td>
<td>58-59</td>
</tr>
</tbody>
</table>

Adapted from pivotal trials by Manns et al., Fried et al., and the National Institutes of Health.
type 1, high viral load, increased body weight, and substantial fibrosis (bridging fibrosis and cirrhosis).24,25 For example, the sustained virologic response for patients with genotype 1 with peginterferon and ribavirin is between 42% and 56%. For patients with genotypes 2 and 3, the sustained virologic response is between 75% and 84%. In patients with genotype 1 and a high viral load, the sustained virologic response is between 26% and 42%. With low viral load, the sustained virologic response was between 52% and 56%. In patients with bridging fibrosis and cirrhosis, the sustained virologic response is between 29% and 43%.24,25 Treatment of patients with compensated cirrhosis must be tempered by the fact that many patients are already thrombocytopenic before starting therapy, and many may be at risk of further decompensation when therapy is instituted. Patients with decompensated liver disease tolerate interferon poorly and have a higher incidence of adverse events55-57; they should not be given interferon.

Nonresponders

By 2015, the number of nonresponders to either interferon/ribavirin or peginterferon/ribavirin seeking retreatment is expected to outgrow the number of patients who are seeking initial therapy. The primary goal of retreatment is to achieve a sustained virologic response. Secondary goals include the prevention of progressive histologic diseases, the regression of fibrosis, a decrease in the risk of hepatocellular carcinoma, and, potentially, a reduction of the risk of hepatic decompensation. The sustained virologic response in interferon/ribavirin nonresponders retreated with peginterferon/ribavirin is between 4% and 12%.58-60

Unfortunately, retreatment options are limited, and their efficacy is low. Options in nonresponders may include peginterferon maintenance therapy or interferon alfacon-1 used in combination with ribavirin. When retreatment nonresponders to interferon or interferon/ribavirin, early virologic response is often assessed at 20 to 24 weeks rather than at 12 weeks.59 In preliminary studies, the results from using interferon alfacon-1 and ribavirin appear promising in nonresponders to interferon/ribavirin and peginterferon/ribavirin.61,62 However, larger trials are needed before this approach is used routinely in clinical practice.

HIV/hepatitis C coinfection

The human immunodeficiency virus and hepatitis C have similar modes of transmission, so rates of coinfection are higher. Several studies have shown that approximately 25% to 30% of all patients infected with HIV in the United States and Europe are also infected with hepatitis C,63,64 and up to 10% of patients infected with hepatitis C may have HIV coinfection.1,64 Response rates to interferon-based therapy appear to be slightly lower in patients with HIV/hepatitis C coinfection compared with patients infected with hepatitis C. As seen in hepatitis C alone, the combination of peginterferon and ribavirin is associated with a higher sustained virologic response than is standard interferon and ribavirin; the sustained virologic response ranged from 27% to 44% with the peginterferon/ribavirin group compared with 11% to 12% with the standard interferon/ribavirin groups.65-67 For patients with genotype 1, the sustained virologic response ranges from 14% to 29% with peginterferon and ribavirin and from 44% to 73% for patients with genotypes 2 and 3.65-67 In one study, the response rates of patients with genotype 4 were analyzed with those of genotype 1.67 Similarly, the response rates in patients with genotypes 2, 3 and 5 were also analyzed together. With treatment for hepatitis C, HIV RNA levels do not appreciable increase. CD4 counts decrease during treatment but return to baseline after completion of therapy. However, the adverse effects of treatment for hepatitis C treatment in HIV coinfected patients lead to high rates of discontinuing therapy.67,68 Patients on highly active antiretroviral therapy may be more susceptible to the hemolytic effects of ribavirin therapy,69 resulting in reductions in its dose or the discontinuation of its use.68 The decision to treat must be weighed against these additional safety concerns in HIV/hepatitis C coinfected patients.

Liver transplant recipients

Hepatitis C is currently the most common indication for orthotopic liver transplantation.70-72 However, recurrence after transplantation is universal.73 Although the 5-year survival rate for transplant recipients with hepatitis C is similar to other patients, more recent data suggest decreased long-term survival.74,75 Moreover, accelerated recurrent hepatitis C infection after transplantation can rapidly result in development of cirrhosis and decompensated disease. Efforts to treat recurrent disease have been hampered by the limited efficacy and adverse effects of current therapies. The combination of interferon and ribavirin has been associated with a sustained virologic response rate of approximately 20%.76-78 and perhaps increasing to approximately 30% with the combination of peginterferon and ribavirin.79,81 However, adverse effects, including rejection of the transplant, are a major concern.71,82,83

Future treatments

A number of therapies for hepatitis C are being studied in early clinical trials84: therapies directed against specific hepatitis C targets (polymerase and protease inhibitors, antisense nucleotides), immunomodulators (histamine, chloride matrix and thymosin alfa), vaccines, alternative interferons (oral interferon alfa, purified multisubtype human interferon alfa, interferon omega and interferon gamma), alternative interferon delivery systems (fusion protein interferon alfa-albumin and transfersome containing interferon
alfa), and ribavirin prodrugs and L isomers. However, no new drugs are expected on the market for several years, and interferon is likely to remain the core of any regimen that becomes available.

Acknowledgments

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References


