INTRODUCTION

The hepatitis C virus (HCV) is a major cause of chronic liver disease with approximately 170 million people infected worldwide and three million in the United States (1,2). In the United States, HCV is now the leading cause for liver transplantation. HCV has a high mutation rate and is able to effectively evade the host immune system. As a result, approximately 80% of acute cases lead to chronic infection. Most of the morbidity associated with HCV occurs in the setting of cirrhosis, which develops in approximately 20%–30% of patients. Through effective screening, the goal is to treat and eradicate HCV and avoid the progression to complications of cirrhosis. Significant advances have been made in the last 15 years in the treatment of HCV infection. Although novel therapies such as protease and polymerase inhibitors are in development, it will be several years before they are likely to impact general clinical practice. This article will therefore summarize current treatment recommendations and also discuss alternative approaches to therapy and populations with treatment challenges.

STANDARD THERAPY

Standard treatment for hepatitis C is the combination of pegylated interferon alfa and ribavirin. Pegylated interferon alfa is administered as a once weekly subcutaneous injection. Interferon alfa is the active moiety and has both antiviral and immunomodulatory effects. Polyethylene glycol is a carrier that decreases excretion and prolongs the half-life, allowing once weekly dosing. Although the antiviral effect of ribavirin is not fully understood, ribavirin disrupts purine metabolism by inhibiting inosine monophosphate dehydrogenase. Standard doses are 1.5 micrograms per kilogram body weight for peginterferon alfa-2b and 180 micrograms for all patients regardless of body weight for peginterferon alfa-2a. Ribavirin doses for genotypes 2 and 3 are usually 800 mg per dose. For genotype 1, the dose of ribavirin is especially important (3). Typical dosing for ribavirin according to the package insert for peginterferon alfa-2a is 1000 mg daily in divided doses for less than 75 kilograms and 1200 mg daily if more than 75 kilograms.

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kilograms. A retrospective analysis of the major trials with peginterferon alfa-2b highlighted the importance of the dose of ribavirin with improved response rates when the patient received more that 10.6 milligrams per kilogram body weight of ribavirin. For genotype 1 patients, many clinicians give between 800 mg and 1400 mg of ribavirin depending upon the weight of the patient. Efficacy of therapy is measured by the sustained virologic response (SVR), which is defined as undetectable HCV RNA as measured by PCR 24 weeks after cessation of therapy. Large randomized trials have reported SVR of 42%–52% for genotype 1 infection and 73%–82% for genotype 2 and 3 infection (4,5).

**DURATION OF THERAPY**

Duration of therapy is dependent on genotype and can also vary depending on initial response to treatment. Standard duration of therapy is 24 weeks for genotypes 2 and 3 and 48 weeks for genotype 1 (3). Several trials have recently looked at shorter therapy lengths for genotypes 2 and 3. Patients with no detectable HCV RNA at week four of therapy when treated for 12 weeks were found to have no significant difference in rates of SVR compared to patients treated for 24 weeks (85% versus 91%) (6). There were fewer adverse events in the group with the shorter length therapy. In a similar noncontrolled trial of 122 subjects, patients with no detectable HCV RNA at weeks four and eight were treated for just 14 weeks, and those with detectable HCV RNA at four and eight weeks were treated for the standard 24 weeks. SVR was achieved in 85/95 (90%) in the 14-week treatment group and 15/27 (56%) in the 24-week treatment group (7).

Conversely, therapy longer than the standard 24 weeks has been found to be beneficial in patients with genotype 1 infection. The TERAVIC-4 Study was presented at the 2004 Liver Meeting. In this study, patients with detectable viral loads at week four were randomized to 48 versus 72 weeks of therapy, and most of the patients in this study were genotype 1. For this group, SVR was obtained in 44% in the 72-week treatment group compared with 28% in the 48-week group (p < 0.0001) (8). Another study randomized genotype 1 naïve patients to 48 weeks versus 72 weeks of therapy with pegylated interferon alfa-2a and ribavirin. Although no difference was observed for SVR between the two groups (53% vs. 54%), patients with detectable HCV RNA at week 12 of therapy were more likely to achieve SVR when treated for 72 weeks (17% versus 29%, p = 0.040) (9). There was no difference in SVR between the two groups in those patients with no detectable RNA at week 12. These findings indicate that longer duration of therapy may be appropriate in a subset of patients infected with genotype 1.

**DIFFICULT TO TREAT POPULATIONS**

**African Americans**

African American patients comprise a population in which the treatment of hepatitis C has been more difficult. In terms of disease characteristics in this population, the National Health and Nutrition Examination Survey from 1999 to 2002 showed a higher prevalence of antibody to HCV in African Americans compared to Caucasians (3.0% versus 1.5%) (2). The highest prevalence of antibody among any race or age group occurs in African American men between the ages of 40 and 49 and occurs at a rate of 13.6%. In addition, African Americans have almost three times higher rates of hepatocellular carcinoma compared to Caucasians (10).

Several studies have shown that African Americans have lower response rates to treatment compared to Caucasians (11–17). Initially, it was hypothesized that these lower response rates in African Americans were due to the increased prevalence of genotype 1 infection in this group (13). When controlling for genotype, Muir, et al found that African Americans have lower rates of SVR compared to Caucasians (19% versus 52%) with therapy with peginterferon alfa-2b plus ribavirin (14). Jeffers, et al examined only patients infected with genotype 1 and demonstrated a non-significant trend towards lower SVR in African Americans versus Caucasians (26% versus 39%) when treated with peginterferon alfa-2a plus ribavirin (15). The VIRAHEP-C study was recently published and confirmed the findings from the previous study. More that 400 patients with genotype 1 infection were treated with peginterferon alfa-2a plus ribavirin and SVR was lower in African Americans compared to Caucasians (28% versus 52%, p < 0.0001) (16) (Table 1).
Differences in SVR have been demonstrated in not only genotype 1, but also in populations with either genotype 2 or 3. In a retrospective analysis, Shiffman, et al examined treatment responses of African Americans and Caucasians with genotypes 2 or 3. Patients had received standard interferon plus ribavirin or peginterferon plus ribavirin. Although the end of treatment, responses were similar with 92% among Caucasians and 82% among African Americans (p = NS), Caucasians were much more likely than African Americans to achieve SVR (84% versus 44%, p = 0.008) (17).

Given that African Americans have lower SVR, recent studies have examined adjustments to the standard dosing of peginterferon and ribavirin. The WIN-R trial examined fixed dose ribavirin at 800 mg compared to weight-based dosing of ribavirin from 800–1400 mg in African Americans with genotype 1 and showed higher rates of SVR in the weight-based arm (21% versus 10%, p < 0.05) (18). The RENEW trial examined the dose of peginterferon alfa and enrolled patients who did not respond to initial therapy with interferon plus ribavirin into either therapy with single dose therapy with peginterferon alfa-2B (1.5 micrograms per kilogram per week) plus weight-based ribavirin or double dose therapy (3.0 micrograms per kilogram per week) plus weight-based ribavirin. Results of this trial showed equivalent rates of SVR in African Americans compared to other groups tested (19).

The reason for the lower response rate in African Americans remains unknown and is the topic of ongoing research. As more novel therapies enter clinical trials, the response rate of African Americans will be an area of interest.

Co-infected with HCV and HIV

In the last several years, treatment of patients with HIV/HCV have become an area of interest, especially in light of data that co-infection with HIV and HCV leads to increased rates of cirrhosis (20). It is estimated that approximately 33%–37% of patients with HIV are also co-infected with HCV (21,22). The high rate of co-infection is likely secondary to common modes of transmission.

Multiple studies have examined different therapies for patients co-infected with HIV and HCV. Torriani, et al demonstrated that 48 weeks of therapy with peginterferon alfa-2a plus ribavirin was superior to peginterferon alfa-2a or interferon alfa-2a plus ribavirin (40% versus 20% versus 12%) (23). Three other studies have compared peginterferon alfa-2a or alfa-2b plus ribavirin to interferon alfa-2a or alfa-2b plus ribavirin and shown similar results with higher rates of SVR with peginterferon plus ribavirin (27%–44% versus 12%–21%) for a total duration of therapy of 48 weeks (24–26). These studies are summarized in Figure 1 and highlight once again that genotype 1 infection has lower response rates (14%–38%).

An important question to consider is whether these therapies can be applied to all patients co-infected with HIV and HCV. Patients in these studies were in general

<table>
<thead>
<tr>
<th>Author</th>
<th>Interferon alfa</th>
<th>Ribavirin dose</th>
<th>African Americans</th>
<th>Whites</th>
<th>P-value</th>
</tr>
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<td>Muir (14)</td>
<td>Peginterferon alfa-2b 1.5 mc/kg/wk</td>
<td>1000 mg first 12 wks, 800 mg wks 13-48</td>
<td>19%</td>
<td>52%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Jeffers (15)</td>
<td>Peginterferon alfa-2a 180 mcg/wk</td>
<td>1000–1200 mg</td>
<td>26%</td>
<td>39%</td>
<td>NS</td>
</tr>
<tr>
<td>Conjeevaram (16)</td>
<td>Peginterferon alfa-2a 180 mcg/wk</td>
<td>1000–1200 mg</td>
<td>28%</td>
<td>52%</td>
<td>&lt;0.0001</td>
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healthier with stable HIV disease. Common exclusion criteria in many of these studies included having a CD4 count less than 200, active opportunistic infections, decompensated liver disease, clinically significant anemia, neutropenia or thrombocytopenia. These are important factors to remember when using the results of these studies for patients infected with HIV and HCV.

Side effects from therapy with peginterferon and ribavirin are important to consider in patients with HIV. One of the above studies reported 11 patients that developed mitochondrial toxicity as evidenced by hyperlactatemia, lactic acidosis or acute pancreatitis. All of these patients had been taking didanosine and were receiving therapy with ribavirin. Because ribavirin is a nucleoside analog, the addition of this drug to patients who are taking didanosine, a nucleoside reverse transcriptase inhibitor, should be avoided (25). Other common side effects seen in these studies included anemia, neutropenia and thrombocytopenia. The additive effect of antiretroviral therapy and HCV therapy may compound this situation and growth factors may be required to achieve reasonable doses of HCV therapy.

End Stage Renal Disease

Approximately 10% of patients with end stage renal disease (ESRD) are infected with hepatitis C (27). Higher rates of mortality are associated with patients who have ESRD and HCV infection compared to those without HCV infection (28,29). HCV infection also increases mortality rates in patients who have undergone kidney transplantation (30,31). These data help explain the rationale for treating HCV infection so that patients receive maximal benefit from kidney transplantation.

Figure 1. Response rates for randomized trials of HCV treatment in patient co-infected with HIV (23–26).
Hepatitis C

Early studies examined treatment of HCV infection after renal transplantation. Some patients in these reports showed graft rejection after initiation of therapy for hepatitis C (32,33). As a result, there has been considerable interest in treatment of HCV before transplantation. Two reviews have examined data from individual studies that have treated HCV in patients with ESRD with unmodified interferon alfa. The first review examined eight studies with unmodified interferon alfa three times weekly for six to 12 months. The combined SVR was 33% for all genotypes and 26% for genotype 1 (34). The second review examined 17 studies that used unmodified interferon alfa with doses ranging from one to 10 million units three times weekly for four to 12 months. The combined SVR was 40% (35). Compared to previous studies of unmodified interferon alfa monotherapy in patients without renal disease, the rates of SVR are much higher in patients with ESRD. However, most of these reports were case series, and it remains unclear if patients with ESRD have increased SVR with interferon alfa monotherapy. One concern with patients with HCV and ESRD has been the risk of HCV therapy. These studies have reported severe side effects with a high rate of early discontinuation. The side effects included pulmonary edema, cerebral hemorrhage, acute pancreatitis, cardiomyopathy, lymphoma, diplopia and severe septic shock (35). The most common reactions reported by one study included flu-like symptoms, leukopenia, depression, confusion and seizures (34).

Currently, the role of peginterferon in therapy for patients with ESRD and HCV infection is under evaluation. One study randomized patients to therapy with pegylated interferon alfa-2b with either 1.0 micrograms per kilogram or 0.5 micrograms per kilogram dosing for 48 weeks (36). The study was terminated prematurely secondary to serious adverse events that occurred in seven out of the 16 people who had already been enrolled. The most common side effects experienced were infection secondary to neutropenia and hypertension. No one in the lower dose group achieved SVR, but 22% of the higher dose group did obtain SVR. Luxon, et al examined the addition of low dose ribavirin to peginterferon alfa-2b 1.0 micrograms per kilogram per week (37). Patients were randomized to peginterferon alone or in combination with ribavirin 200 mg weekly. If the hemoglobin could be maintained greater than 9 gm/dl, the dose of ribavirin could be increased to twice weekly or three times weekly. One patient had a 2-log reduction at week 12 but had persistent virus at 48 weeks. Seven patients discontinued due to severe adverse effects. Based on these studies, treatment of patients with ESRD and HCV should be approached with caution and within a research protocol.

CONCLUSION

Although great strides have been made in the treatment of HCV, challenges remain. The current response rates are suboptimal in patients with genotype 1, African Americans, HIV/HCV, and ESRD. Current strategies include improving the response through new approaches with current therapies while waiting for development of novel therapies. For all these patient groups, greater understanding of their HCV treatment might provide insight that will aid all patients with HCV. Further research in these areas will hopefully lead to better treatment strategies for HCV and ultimately reduce morbidity and mortality from this infection.

References

8. Sanchez-Tapias JM, Escartin P, Enriquez J, et al. Longer treatment duration with peginterferon alfa-2a (40KD) (Pegasys) and ribavirin (Copegus) in naive patients with chronic hepatitis C and
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