Antiviral Therapy for the Management of Hepatitis C

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Hepatitis C is a major cause of liver-related morbidity and mortality throughout the world. Over 170 million cases are identified worldwide,[1] with approximately 2% of the US population (4 million people) having been infected.[2] Current estimates suggest that approximately 2.7 million people in the United States are chronically infected,[2] but this may be an under-representation, as specific at-risk groups (eg, the homeless and prison populations) were not accounted for in this analysis.[3] Although the incidence of acute hepatitis C is decreasing, largely due to better screening of the blood bank supply and enacting more stringent universal precautions, the recognition of patients with chronic hepatitis C continues to rise.[2] Natural history studies have demonstrated that the rate of progression to cirrhosis after 20 years of chronic infection approaches 20%,[4] with a significant proportion developing end-stage liver disease. As a result, hepatitis C is currently the leading cause for liver transplantation in this country.[5] Furthermore, up to 5,000 inhospital deaths occur annually in the United States due to hepatitis C complications.[2] In addition to liver-related complications, extrahepatic manifestations of chronic hepatitis C virus (HCV) infection are common and occur in 30% to 40% of patients (**Table 1**). Recently, great strides have been made in our understanding of this virus, which has led to increased treatment-related viral eradication rates with potential for further improvement in the near future. The following article provides an update on the current management of chronic HCV infection and outlines future trends in therapy.

PREVIOUS THERAPEUTIC TREATMENT MODALITIES FOR HCV

Significant advances have been made in therapeutic efficacy and treatment modalities over the past 10 years. Initially, treatment involved 6 months of interferon-α alone given 3 times weekly for 24 weeks with sustained viral response (SVR) rates (ie, the absence of detectable viremia 6 months after completion of therapy) of only about 10% to 15%.[6] Patients were then treated with interferon alfa for 48 weeks, with improvement in overall SVR to 13% to 19%.[6] Subsequently, it was demonstrated that ribavirin was effective at correcting aminotransferase levels in some patients with chronic hepatitis C, and in those patients there appeared to be improvement in liver biopsy specimens.[7] As a result of these findings, ribavirin was eventually tested in combination with interferon, resulting in SVR rates of 40% to 45%.[8] More recently, it has been shown that by attaching the inert polymer polyethylene glycol (PEG) to the interferon molecule, the rate of absorption following subcutaneous injection as well as renal and cellular clearance are reduced, allowing the steady state concentration of drug in plasma to be prolonged. This prolongation results in a decreased dosing regimen to once weekly and increased viral clearance rates.[9]

CURRENT THERAPY FOR HCV

Current routine treatment is with a combination of pegylated interferon (or peginterferon) and ribavirin. Two types of peginterferon are available, peginterferon alfa-2a and peginterferon alfa-2b. Several differences exist between these 2 molecules. Peginterferon alfa-2a (Hoffmann La-Roche, Nutley, NJ) has a branched PEG side chain with a molecular weight of 40 kDa. Comparatively, peginterferon alfa-2b (Schering Corporation, Kennilworth, NJ) has a linear PEG side chain with a molecular weight of 12 kDa. The differences in the inactive side chains result in different pharmacokinetic profiles and modes of clearance,[1] but at present the

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Table 1. Extrahepatic Manifestations of Chronic Hepatitis C Infection

Hematologic disorders
Mixed cryoglobulinemia
Monoclonal gammopathies
Lymphoma
Autoimmune disorders
Hypothyroidism
Sialoadenitis
Idiopathic thrombocytopenic purpura
Ophthalmologic disorders
Corneal ulcers (Mooren's ulcers)
Uveitis
Scleritis
Sicca syndrome
Renal disorders
Membranoproliferative glomerulonephritis
Membranous nephropathy
Dermatologic disorders
Porphyria cutanea tarda
Leukocytoclastic vasculitis
Lichen planus

Table 2. Three Randomized Controlled Trials of Therapy with Combination Pegylated Interferon and Ribavirin

	Manns et al[10]*	Fried et al[11]*	Hadziyannis et al[12]*
Treatment	Peginterferon alfa-2b plus 800 mg ribavirin	Peginterferon alfa-2a plus 1000–1200 mg ribavirin	Peginterferon alfa-2a plus 1000–1200 mg ribavirin
Patients, n	511	453	436
Age (mean years)	43	42.8	43
Viral load (> 2 million copies/mL)	68%	65%	68%
Overall SVR rates	54%	56%	63%
Genotype 1	42%	46%	52%
Genotype 2 or 3	82%	76%	80%
Weight (mean kg)	82	79.8	77
Stage 3–4 fibrosis	29%	12%	26%

SVR = sustained viral response.

*Only one arm of study.

clinical significance of these differences are unknown.

The efficacy of these 2 interferon compounds in combination with varying doses of ribavirin in treatment-naive patients with chronic hepatitis C have been demonstrated in 3 large randomized trials (**Table 2**).[10–12] Overall, the sustained viral response rates are now approaching 60%. When divided into specific genotypes, the SVR for genotype 1 is 42% to 56%, and the SVR for genotypes 2 and 3 is 76% to 82%.[10–12]

The current recommendation is to tailor therapy to specific genotype. Although many genotypes of HCV have been identified, this article will focus on genotypes 1, 2, and 3. For patients with genotype 1, combination therapy with pegylated interferon and ribavirin is continued for 48 weeks. If using peginterferon alfa-2b, then typically the dose of interferon is weight-based at 1.5 μg/kg/wk. If using peginterferon alfa-2a, then the dose of interferon is fixed at 180 μg/wk.[3] Ribavirin is typically dosed at 800 to 1200 mg daily, depending on the patient's weight. These doses are generalizations, and care should be taken to tailor therapy based on pretreatment blood counts and serum creatinine levels because these drugs have significant side effect profiles.

Therapy for genotype 2 or 3 patients is typically the same, except for recent evidence suggesting that fixed-dose ribavirin at 800 mg daily is equally efficacious as higher doses.[12] Therapy should be continued for only 24 weeks because prolonged treatment in these patients does not increase the SVR.

Assessing Response to Therapy

Given that response rates do not reach 100% at present, several investigators have evaluated independent predictors of response to therapy (**Table 3**).[7,10–12] As previously mentioned, it is now evident that genotype 1, while the most common genotype found in the United States (~70%), is the most difficult to treat. Alternatively, genotypes 2 and 3, found in 15% to 20% of cases, respond much more favorably to treatment and may not require as long a duration of therapy.[10–12] Additionally, low viral loads (< 2 million copies/mL) and age (< 40 years) predict better response to therapy.[10,11] Alternatively, it appears that African American race, stages 3 or 4 of fibrosis, high viral load, and age older than 50 years are negative predictors of response to therapy.[7,10–12]

Treatment Response and Strategies for Patients Naive to Interferon-Based Therapy

Once treatment has been initiated with peginterferon and ribavirin, the response to therapy at week 12 can be predicted by measuring the viral load in serum

Table 3. Clinical Predictors of Favorable Response to Peginterferon and Ribavirin Combination Therapy

Age < 40 years[10,11]
Non–African American race[7]
Genotypes 2 and 3[10–12]
Viral load < 2 million copies/mL[10]
Fibrosis stage 1–2[10]
Weight < 85 kg[10,11]

(**Figure**).[13] If at least a 2-log drop (100-fold decrease) in virus is found or the virus is undetectable, these patients should be continued on therapy, as the overall SVR rates for these patients approaches 70%. Alternatively, if the viral load has not dropped by at least 2 logs from baseline, therapy should be discontinued, as the percentage of patients who will develop an SVR is less than 2%.[13]

Additionally, a recent retrospective evaluation of several of the larger treatment databases demonstrated that adherence to combination therapy for the duration of treatment is critical in achieving an optimum SVR rate.[14] If patients took 80% of their medication for 80% of the time, the overall SVR rate climbed to 72%. This finding should encourage health care providers with patients who have chronic hepatitis C to treat the side effects of medication aggressively in order to avoid reducing doses if possible, and to counsel their patients on the need to take their medication regularly.

Treatment of Prior Nonresponders or Relapsers

The overall response to therapy to prior therapeutic modalities was poor. Subsequently, there are many patients who have been treated with interferon monotherapy or combination interferon-ribavirin in the past but either relapsed, as evidenced by a negative viral load at the end of treatment but now with detectable virus on follow-up, or were nonresponders to therapy. Physicians now must consider re-treating these patients with the newer peginterferon in combination with ribavirin.

Recent studies have evaluated the response to re-treatment with combination peginterferon and ribavirin (**Table 4**).[15–17] It now appears that those with a prior response to a therapy but subsequently relapse have the highest chance of achieving an SVR with the newer therapy. Conversely, if a patient was treated with combination interferon-ribavirin and was considered a nonresponder, re-treatment with combination peginterferon-ribavirin results in a SVR in only 6% to 10% of the cases.[15]

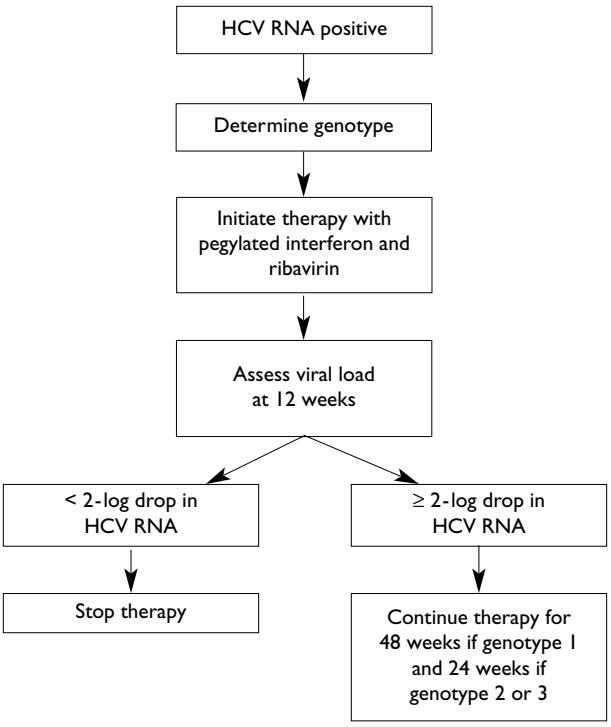

Figure. Therapeutic algorithm for treatment-naive patients diagnosed with hepatitis C virus (HCV).

TREATMENT OF SPECIAL POPULATIONS

Chronic HCV Patients with Normal Alanine Aminotransferase Levels

Evidence suggests that approximately 30% of patients with chronic hepatitis C will have persistently normal alanine aminotransferase levels. The majority of these patients will have mild disease on histopathologic assessment, but a few will have more advanced stages of fibrosis. Response rates to combination pegylated interferon and ribavirin appear to be similar to those in patients with abnormal liver enzymes.[18]

HIV/HCV Co-infection

The prevalence of HCV co-infection in patients with HIV has been estimated to be between 16% to 25%.[19] Epidemiologic studies suggest that these patients have a much more rapid progression of hepatic fibrosis. Since the development of highly active antiretroviral therapy (HAART) in the late 1990s, liver disease, including HCV infection, has emerged as a leading cause of morbidity and mortality. Treatment with combination pegylated interferon and ribavirin have demonstrated SVR rates of 26% to 40%, but discontinuation rates are significantly higher, ranging from 12% to 39%.[19] Consideration should be given to the type of HAART given,

Table 4. SVR Rates Comparing HCV Modalities in Previously Treated Patients*

Treatment Groups	SVR Rate (%)		
	Jacobson et al[15]	Lawitz et al[16]	Shiffman et al[17]
Interferon monotherapy nonresponders	16, 27†	13, 14‡	28§
Interferon-ribavirin relapsers	32, 47†	26, 20‡	Not included
Interferon-ribavirin nonresponders	6, 10†	5, 10‡	12§

SVR = sustained virologic response.

*SVR rates in patients treated with combination peginterferon and ribavirin who were either nonresponders to previous interferon monotherapy or relapsers or nonresponders to combination therapy with interferon-ribavirin.

†The first percentage is the result of treatment with peginterferon alfa-2b 1.0 μg/kg/wk plus ribavirin 1000 to 1200 mg/d. The second percentage is the result of treatment with peginterferon alfa-2b 1.5 μg/kg/wk plus ribavirin 800 mg/d.

‡The first percentage is the result of treatment with peginterferon alfa-2b 1.0 μg/kg/wk plus ribavirin 800 mg/d for 48 weeks. The second percentage is the result of treatment using induction therapy with peginterferon alfa-2b 1.5 μg/kg/wk plus ribavirin 1000 to 1200 mg/d for 12 weeks followed by 36 weeks with peginterferon alfa-2b dosed at 1.0 μg/kg/wk plus ribavirin 800 mg/d.

§Results of treatment with interferon alfa-2a 180 μg/wk plus either 1000 to 1200 mg ribavirin, depending on weight for 48 weeks.

in that major adverse events, to include mitochondrial injury leading to liver failure, lactic acidosis, and pancreatitis have been reported, especially in patients taking dideoxyinosine with ribavirin. Ribavirin is also a nucleoside analogue and interferes with dideoxyinosine metabolism, increasing the drug level and toxicities. Currently, optimal dosing regimens are not clearly defined, and relapse rates may be higher.

LIVER TRANSPLANTATION

Progression to cirrhosis occurs in 20% to 30% of patients over a 20-year period.[4] It has been estimated that hepatic decompensation, as manifested by ascites, varices, spontaneous bacterial peritonitis, hepatic encephalopathy or coagulopathy, occurs at a rate of up to 6% per year, with development of hepatocellular carcinoma occurring in up to 3% annually.[20] Consequently, end-stage liver disease due to hepatitis C remains the primary reason for liver transplantation in this country.[5] Unfortunately, viremia recurrence is almost universal, and fibrosis progression is often accelerated.

Treatment results with antiviral therapy after liver transplantation is limited and mainly comprises uncontrolled observation studies. Adverse events are common. As a result, attention has recently focused on treating cirrhotic patients, both compensated and decompensated with antiviral therapy, prior to consideration for liver transplantation. SVR rates of 11% to 50% have been shown with compensated disease.[12,17] However, cirrhotic patients require close monitoring due to the high incidence of anemia, neutropenia, and thrombocytopenia, and therapy is best instituted at experienced centers with liver transplant affiliation. At present, while promising data exists, treatment of patients with evidence of decompensated disease should be undertaken in the context of a clinical trial.

MANAGING SPECIFIC ANTIVIRAL THERAPY SIDE EFFECTS

Anemia

Anemia is commonly seen in patients treated with combination pegylated interferon and ribavirin. In fact, more than 50% of patients will experience at least a 3 g/dL drop in hemoglobin during therapy,[21] largely within the first 2 to 6 weeks. Pegylated interferon alfa causes bone marrow suppression of all cell lines, including red cells, and ribavirin causes both a dose-dependent red cell hemolysis due to oxidative stress and suppression of erythropoiesis. Anemia often results in impaired functional capacity and may lead to exacerbation of underlying cardiopulmonary problems.

Historically, dose reductions in ribavirin were advocated when the hemoglobin level dropped to 10 g/dL and discontinued at a hemoglobin level of 8.5g/dL. However, recent evidence has demonstrated that maintaining ribavirin dosing at greater than 10.6 mg/kg/d results in improved SVR.[10] Furthermore, as previously noted, evidence suggests that patients have a greater chance of achieving an SVR if they are able to maintain their ribavirin and pegylated interferon doses at 80% of baseline for 80% of the time.[14] Consequently, recombinant human erythropoietin subcutaneous injections have become routine in anemic patients receiving combination therapy in an effort to prevent ribavirin dose reductions. Recently, it has been shown that once weekly, subcutaneous administration of 40,000 U of epoetin alfa is capable of preventing ribavirin dose reductions, improves quality of life, and hemoglobin levels.[22] Further study is needed, however, to confirm that epoetin alfa therapy results in enhanced SVR, as implied by the ability to maintain ribavirin dosing.

Neutropenia

Neutropenia is a common side effect of pegylated

interferon therapy. Typically, neutrophil levels drop 30% to 50% from baseline. Fortunately, infection as a result of interferon-induced anemia is uncommon. Currently, the dosage is reduced if the absolute neutrophil count drops below 750 μL.[23,24] While data are lacking to support its usage, recombinant human granulocyte colony-stimulating factor is widely used to maintain neutrophil counts. Future trials are needed to assess the efficacy of granulocyte colony-stimulating factor dosing versus interferon dose reductions.

Depression

Neuropyschiatric side effects are common with interferon-based therapy. Depression may occur in up to 30% of patients and can be severe. Clinically, patients may present with mood disturbances, apathy, anhedonia, fatigue, insomnia, sexual dysfunction, or cognitive impairment. Suicidal ideation may occur but tends to be infrequent. Most often, depressive symptoms begin in the first 12 weeks of therapy.[25] Although a history of depression is not a contraindication to interferon-based therapy, a careful analysis of the patient's current state of mind is warranted. Recommended interview and screening tools include the Beck Depression Inventory, the Center for Epidemiologic Studies Depression Scale,[26] or the Montgomery-Asberg Depression Rating Scale. Consultation with a behavorial health specialist, such as a psychiatrist or psychologist, should be considered in patients on antidepressant therapy with ongoing psychiatric symptoms. Studies have demonstrated that the selective serotonin reuptake inhibitors are effective in treating depression in patients taking interferon-based therapy.[27,28]

Contraindications to Therapy

Ribavirin is teratogenic and embryocidal, and as a result, women who are pregnant or thinking of becoming pregnant should not be treated. Additionally, ribavirin accumulates in gonadal tissue and may still be present 6 months after cessation of therapy. Subsequently, male patients should be counseled appropriately as well.

Renal impairment, as defined by a creatinine clearance rate below 50 mL/min, is a relative contraindication to therapy, as both interferon and ribavirin are excreted renally. Toxic accumulation of the drug may occur, leading to severe hematologic consequences. Patients with severe cardiovascular disease should be approached with caution due to the likelihood of developing anemia while on therapy. Furthermore, patients with psychiatric disorders including severe depression, suicidal or homicidal behavior, or ongoing substance abuse should be excluded from treatment.

FUTURE THERAPEUTIC OPTIONS

Although significant progress has been made in the past 10 years (from 10% viral clearance rates to almost 60% at present), there is still much room for improvement. Progress is needed, not only in increasing the percentage of patients who achieve an SVR, but in reducing the side effect profile of therapy.

Current treatment with interferon-based therapy is aimed at modulating the human body's immune response. Newer therapies are targeting the virus directly in an attempt to cease viral replication. Preliminary results seem encouraging. Specifically, researchers are targeting specific proteases, helicases, and polymerases that result in cessation of viral replication.[29] These therapeutic modalities are still in phase 1 and 2 trials, but optimists speculate that they may be ready for clinical use within the next 5 to 7 years.

CONCLUSION

The 2002 National Institutes of Health consensus conference guidelines for treating patients with HCV infection recommend that all patients should be considered candidates for treatment, including those with normal aminotransferase levels or mild disease on biopsy.[3]

The author encourages health care providers who plan on treating patients with hepatitis C to evaluate each case independently, carefully considering each individual's predictors of virologic response and the likelihood the patient is going to be able to comply with the therapeutic regimen.[3] Once this has been accomplished and the decision has been made to treat the patient, both pegylated interferon products appear to have similar efficacy for each genotype, and the decision on which product to use appears arbitrary at this point. Future trials may more clearly define a unique niche for each pegylated interferon product. Finally, it is important to understand that future therapies are on the horizon and offer the potential for even greater success. **HP**

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