THE CLINICIAN’S COMPANION VII: Expert Perspectives on Contemporary Clinical Issues in Hepatitis C

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Dear Colleague:

We are pleased to present the latest Clinician’s Companion, an up-to-date 64-page monograph on the latest developments in hepatitis C.

The management of hepatitis C virus (HCV) continues to be a challenge to clinicians, since many HCV patients do not experience a sustained virologic response to therapy. Patients with HCV infection can go on to develop cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC), and death. Due to the large pool of patients with chronic HCV infections, the Centers for Disease Control and Prevention (CDC) predicts that HCV-related complications may double or triple within the next 10 to 20 years. Due to these figures and the large pool of patients presenting with this disease, more information is necessary for healthcare providers to appropriately diagnose and treat this disease. The American Liver Foundation (ALF) has recently stressed the importance of testing those at risk for HCV, since more than 80% of the 3.9 million Americans with HCV are unaware that they are infected. The CDC, in the National Hepatitis Prevention Strategy indicated that it is critical to educate healthcare professionals to identify persons at risk to diagnose these individuals, and to treat them.

The Clinician’s Companion VII: Expert Perspectives on Contemporary Clinical Issues in Hepatitis C features the shared perspectives of experts confronting key issues, many of which are faced by clinicians in everyday practice. This information incorporates scientific advances made over the past year and their clinical implications. You will have an opportunity to learn about new findings in epidemiology, diagnosis, management of side effects associated with HCV therapies, the relationship of HCV and HCC, and strategies for managing hard-to-treat patients and those with advanced disease.

During the past 7 years, this successful series has provided gastroenterologists, hepatologists, and allied health professionals with state-of-the-science education that has immediate clinical relevance. Recognition for the Clinician’s Companion series has grown over the years, and clinicians anticipate each year’s edition as an important reference they will use in the treatment of HCV infection.

We hope you find this monograph helpful and informative.

Sincerely,

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Target Audience
This CME activity is designed for gastroenterologists and hepatologists who diagnose and treat patients with chronic hepatitis C virus (HCV) infection and who need immediate and practical information to address real-world clinical challenges associated with the care of their patients. It is also designed for physicians who may be called upon to provide basic education on hepatitis C to their communities. An intermediate to advanced level of expertise in caring for patients with HCV infection is assumed.

Activity Goal
The goal of this activity is to provide clinicians with a solid foundation of knowledge and practical clinical skills to apply in practice, and the latest diagnostic, monitoring, and treatment strategies.

Learning Objectives
Upon completion of this activity, physicians should be able to:

- Discuss advances and new directions in HCV diagnosis, monitoring, and treatment.
- Use diagnostic procedures, including various HCV assays and tests to assess the degree of liver fibrosis, in a timely fashion and in accordance with the latest guidelines to identify infected individuals and monitor treatment response.
- Formulate effective treatment strategies for patients with chronic HCV infection.
- Promote adherence to anti-HCV therapy by emphasis on patient education and the management of side effects.
- Address the unique needs of specific patient groups, including HIV/HCV-coinfected patients, patients with advanced kidney or liver disease, nonresponders to first-line therapy, diabetics, and others.
- Provide appropriate treatment and monitoring to patients with advanced liver disease.
- Develop an overall care plan for patients with advanced HCV-related liver disease who require liver transplantation.

CME Information

Statement of Accreditation
Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation
Projects In Knowledge designates this educational activity for a maximum of 3 Category 1 credits toward the AMA Physician’s Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This activity is planned and implemented as an independent CME activity in accordance with the ACCME Essential Areas and Policies.

Successful completion for up to 3 hours of CME credit requires a passing score of 70% or higher on the posttest. Full instructions for submission are included on the posttest enclosed in this monograph.

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For complete prescribing information on the products discussed during this CME activity, please see your current Physicians’ Desk Reference (PDR).

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Faculty
Peginterferon/ribavirin has been the standard of care for treating hepatitis C for several years now. Sustained virologic response (SVR) provides long-term durable benefits and remains the primary goal of therapy. In initial clinical trials, SVR was achieved by approximately half of all patients. Since this combination became available, we have learned how to individualize treatment to enhance these response rates and maximize outcomes.

A number of factors that affect response rates are fixed and not modifiable, including genotype, fibrosis, viral level, age, gender, and body weight. However, recently discovered predictors of response include treatment adherence and ribavirin dosage, which clinicians can influence. Other recently recognized factors that affect response include ethnicity and the presence of steatosis. With this increased recognition of the importance of adherence, especially early in the treatment period, physicians have begun to focus on strategies to keep patients on treatment. This process begins with appropriate selection of treatment candidates and timing of treatment initiation. Pre-existing conditions, including substance abuse and depression, should be identified and controlled before antiviral therapy is initiated. Patient education is an important component of management. Along with information about the disease and treatment regimen, patients should be told of the importance of adherence and consequences of nonadherence. Clinicians should ascertain whether the patient has a support network, and teach family members to help patients cope with the illness and treatment. Other strategies to promote adherence include pill organizers, reminders, accessible refills, and the development of pre-filled, easy to use injectable delivery systems.

Side effects are among the biggest factors affecting adherence. It is important for physicians to be proactive about managing side effects and teaching patients how to relieve symptoms. We are increasingly learning the value of adjunctive therapies in managing side effects without resorting to dose reductions or treatment discontinuations, which can limit the effectiveness of therapy.

The Clinician’s Companion VII brings you up to date on the latest knowledge about hepatitis C, predictors of response, and strategies for improving treatment outcomes. The following chapters discuss how response can be limited by steatosis and poor adherence, and how side effects can impact quality of life and have serious consequences. New information about adjunctive therapies, such as darbepoetin and epoetin, will be presented. For patients who do not achieve a sustained response despite our best efforts, we will consider maintenance therapy to reduce progression, and look down the road toward newer therapies that are showing promise in early clinical trials. Finally, for patients with the most advanced disease, we will consider the current state of liver transplantation and the risk of and need to monitor for hepatocellular carcinoma. As in years past, this Clinician’s Companion should be a valuable educational resource that reviews the most up-to-date information about hepatitis C and promotes the best possible outcomes for your patients.
Key Points

- Hepatic steatosis is commonly associated with chronic hepatitis C (CHC).
- Hepatic steatosis likely leads to progression of fibrosis in patients with CHC.
- The presence of coexistent steatosis/steatohepatitis appears to negatively affect early and sustained virologic response (SVR) rates.
- Immune system responses and interferon (IFN) bioavailability may be altered in the setting of coexistent hepatic steatosis.

Introduction

CHC affects more than 4 million people nationwide and is the leading indication for liver transplantation. Presently, therapy for hepatitis C includes peginterferon (PEG IFN) and ribavirin (RBV) combination therapy, with SVR rates of 54% to 63%.

Factors influencing response to therapy include age, duration of infection, ethnicity, gender, genotype, fibrosis stage, and body weight. Recent interest has focused on hepatic steatosis and how fatty liver may impact response to antiviral therapy.

Etiology of Coexistent Hepatic Steatosis

The histopathologic finding of hepatic steatosis in patients with CHC has been well documented and occurs in approximately 50% of patients. However, the pathogenesis of concurrent hepatic steatosis in CHC is quite complex and appears to involve multiple mechanisms. Some are host dependent, relating to metabolic factors, alcohol intake, and medications, while others are virally mediated (See Fig. 1.1).

Figure 1.1. Proposed Mechanisms for Coexistent Steatosis and CHC.

The prevalence of nonalcoholic fatty liver disease (NAFLD) in the United States has been suggested to be about 20% of the population. Clinical factors commonly found in patients with NAFLD include obesity, visceral adiposity, hypertension, insulin resistance, and diabetes mellitus. Similar findings have been shown in CHC patients with hepatic steatosis. This similarity is not surprising given the prevalence of both diseases in our population. In fact, evidence suggests that the presence of coexistent CHC and hepatic steatosis is 2.5-fold higher than would be expected to occur if they were independent processes. Recently, the presence of coexistent steatohepatitis has been described histopathologically by two separate groups and appears to occur in 5% to 10% of biopsy specimens.

CHC affects host metabolic factors and may directly lead to insulin resistance, independent of obesity, as well as β-cell dysfunction. In fact, Shintani and colleagues, utilizing transgenic mice, have shown that hepatitis C viral core protein induces hepatic insulin resistance. Epidemiologic studies confirm these findings as several groups have demonstrated an association between CHC and diabetes mellitus. Furthermore, insulin sensitivity has been shown to improve with IFN therapy.

Hepatic steatosis may also occur through additional virally mediated pathways involving the hepatitis C viral core and NS-5 proteins. Animal models and studies of transfected cells in culture have shown that there is impaired fat trafficking, specifically decreased very low-density lipoprotein secretion, in part, through inhibition of microsomal triglyceride transfer protein activity. In addition, hepatitis C core protein induces oxidative stress via mitochondrial injury. This effect is largely seen in patients infected with genotype 3 virus. Furthering this concept, human studies have shown that the amount of steatosis correlates with the level of viral replication; viral eradication leads to resolution of steatosis in patients infected with this genotype, and there is a return of steatosis with relapse of virus after treatment.

Hepatic Steatosis and Steatohepatitis Decrease SVR Rates

The response to antiviral therapy in patients with hepatitis C and hepatic steatosis is an area of growing interest. Data from several retrospective analyses are
early virologic response in patients with steatosis than those who did not respond to antiviral therapy. Early virologic response in patients with steatosis was also decreased: 71% versus 42% respectively. In contrast, genotype 3-infected patients with coexistent steatosis did not have a decrease in SVR.

While the impact of coexistent steatosis on SVR rates is becoming clearer, there are few data on the impact of concomitant steatohepatitis in patients with CHC treated with antiviral therapy. Recently, we retrospectively analyzed the SVR rates of patients with either significant steatosis (>33%) or coexistent steatohepatitis and CHC, as defined by Brunt and colleagues, versus a group of controls with CHC and <33% steatosis (Fig. 1.2). The overall SVR was 28% versus 44%, respectively (See Fig. 1.2). Interestingly, patients infected with genotype 2 or 3 had a significantly decreased SVR as well, contrasting with previous retrospective data showing no decrease in SVR in genotype 3 patients. This finding is likely explained by the fact that our patients infected with genotype 3 all had coexistent steatohepatitis. Mechanisms for this decreased response to therapy are not fully understood, but two possible explanations include progression of fibrosis in the presence of coexistent steatosis or steatohepatitis, and impaired utilization or hepatic metabolism of IFN.

Increased Fibrosis

Effect of coexistent steatosis on progression of fibrosis has been debated. Earlier studies demonstrated that the presence of hepatic steatosis was associated with increased fibrosis, with higher grades of steatosis correlating with more advanced stages of fibrosis. Subsequently, a correlation of fibrosis progression with worsening hepatic steatosis was demonstrated. Conversely, among a French cohort of CHC patients, no association was found. However, in a recent study involving patients from the United States, weight loss improved both steatosis and fibrosis.

Further studies have suggested a genotype-specific association between steatosis and fibrosis. Two European studies demonstrated a fibrosis association only in patients infected with genotype 3 virus. However, a subsequent study from the United States revealed no fibrosis association in patients with hepatic steatosis infected with genotype 3 virus. These differences in study outcomes are likely the result of differences in study populations, as North American countries tend to have populations with higher BMIs than European countries, and the ratio of genotype 1 to genotype 3 patients is different.

Explanations for how steatosis contributes to fibrosis progression are hypothetical, but the mechanism likely relates to both host and virally mediated factors. Patients who are overweight with visceral adiposity may develop fibrosis in a similar pathophysiologic pattern to that seen in nonalcoholic steatohepatitis. Simplistically, this is thought to occur through activation of quiescent hepatic stellate cells via increased oxidative stress and subsequent lipid peroxidation. In addition, in CHC patients with steatosis, increased cellular apoptosis may enhance fibrosis progression through stellate cell activation. Another mechanism may involve the satiety hormone leptin. Romero-Gomez and colleagues recently showed a correlation between serum leptin levels and steatosis and fibrosis in patients infected with genotype 1. Leptin has been shown to be decreased in patients infected with genotype 3 virus. Leptin levels and steatosis and fibrosis in patients infected with genotype 3 virus. The overall SVR was 28% versus 44%, respectively (See Fig. 1.2). Interestingly, patients infected with genotype 2 or 3 had a significantly decreased SVR as well, contrasting with previous retrospective data showing no decrease in SVR in genotype 3 patients. This finding is likely explained by the fact that our patients infected with genotype 3 all had coexistent steatohepatitis. Mechanisms for this decreased response to therapy are not fully understood, but two possible explanations include progression of fibrosis in the presence of coexistent steatosis or steatohepatitis, and impaired utilization or hepatic metabolism of IFN.
profibrogenic, and up-regulation of leptin signaling may lead to fibrosis progression. Other mechanisms for fibrogenesis, especially in genotype non-1 patients, are likely but have yet to be fully elucidated.

**Decreased Effectiveness of Antiviral Therapy**

Current antiviral therapy relies on up-regulation of the innate immune system to effectively eradicate CHC infection. Recent proposals for the decreased response to antiviral therapy in obese CHC patients with coexistent steatosis or steatohepatitis include an altered immune response, fixed drug dosing, and decreased bioavailability of IFN (Fig. 1.3, see page 8). Obese patients are characteristically insulin resistant, and CHC infection has been associated with insulin resistance as well. It has been proposed that obesity, and thus insulin resistance, may decrease the efficacy of antiviral therapy through altered immune responses. This may occur via a leptin-mediated process. Serum leptin levels have been shown to be higher in patients with hepatitis C virus infection than in controls, with concentrations decreasing in sustained virologic responders. In addition to being a satiety hormone, leptin has been shown to bind to T cells and may up-regulate the Th1 response. Mechanistically, IFN is thought to augment the Th1 response. Subsequently, in patients who are insulin resistant, and therefore likely to be leptin resistant, the efficacy of IFN may be diminished.

Several studies have demonstrated that the efficacy of antiviral therapy is related to the dose administered. In fact, previous studies have shown that fixed, rather than weight-based dosing, irrespective of the type of IFN, leads to decreased response to therapy in obese patients. However, pharmacokinetic studies of PEG IFN alfa-2a (which is administered at a fixed dose) have demonstrated that the serum levels of drug are higher at all time points than weight-based PEG IFN alfa-2b. This is understandable given the smaller volume of distribution and lower clearance rates. The effect of fixed dosing versus weight-based dosing, while significant, may be small.

In addition, the presence of steatosis may alter hepatocyte function and impair the ability of IFN to interact with the hepatocyte directly, leading to decreased antiviral efficacy. Indeed, obesity, which is directly associated with hepatic steatosis, leads to decreased 2’,5’-oligoadenylate synthetase levels, indicating decreased IFN activity.

**Summary**

Coexistent steatosis is frequently seen in patients with CHC. Both host and virally mediated factors are thought to contribute to the development of hepatic steatosis. The efficacy of current antiviral therapy appears to be altered by the presence of hepatic steatosis, predominantly in patients infected with genotype 1. Potential mechanisms for this altered response have been suggested and include progression of fibrosis, altered immune responses, and decreased bioavailability of IFN. Further studies evaluating the modulation of hepatic steatosis prior to initiation of antiviral therapy seem warranted given these preliminary insights. In addition, a clearer understanding of the mechanisms by which steatosis affects antiviral therapy is needed.

**REFERENCES**

II. OVERVIEW OF SIDE EFFECT MANAGEMENT

F. Fred Poordad, MD

Key Points

- Virtually all patients treated with peginterferon (PEG IFN) and ribavirin (RBV) experience side effects, which are largely mild and tolerable.
- Side effects can reduce quality of life and can limit the effectiveness of treatment if they necessitate dose reduction or discontinuation.
- Patients should be informed that side effects are expected and should be educated about strategies for side effect management.
- Judicious use of adjuvant therapies, such as antidepressants, analgesics, over-the-counter remedies for gastrointestinal side effects, and other useful therapies should be favored over dose reduction or treatment discontinuation whenever feasible.
- With careful monitoring and aggressive side effect management, most patients can successfully complete therapy.

Introduction

Therapy for hepatitis C virus (HCV) has progressed greatly over the past decade, to the point where the majority of patients can achieve sustained response if dosed properly, and if adherence to the regimen is maintained. The standard-of-care treatment is a combination of PEG IFN and RBV, both of which have a wide variety of potential adverse events associated with them. While the majority of these side effects are mild and tolerable, some are potentially serious. The following text describes common nonhematologic adverse events associated with therapy, along with practical approaches to dealing with them. (Please refer to the chapter “Effective Hematologic Side Effect Management in Treatment of Chronic Hepatitis C” elsewhere in this monograph for a detailed discussion of hematologic side effects.)

Constitutional Symptoms and Fatigue

IFNs are associated with flulike symptoms, including headache, myalgias, arthralgias, fever, nausea, and asthenia. These symptoms are class effects of all IFNs, and there is no IFN product that is not associated with them. The symptoms are related to IFN-induced cytokine products, which are the effector proteins necessary for viral clearance. Similar side effects have been noted with other interleukin molecules.¹

While symptoms vary in severity between patients, they generally wane in intensity after the first few injections of PEG IFN alfa-2b. Conversely, since the steady-state serum concentration of PEG IFN alfa-2a takes longer to achieve, peak side effects are often noted in the second to third month of therapy.

Patient preparation involves education, and specifically, instructions regarding when to inject (ie, day versus night, day of the week), which should be tailored to the patient’s work schedule. Patients should be told to expect the onset of side effects within 4 to 6 hours of injection, and the peak severity within 36 hours of injection. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are useful in symptom control, along with adequate hydration (Table 2.1, see page 12).

Fatigue is one of the most common symptoms of HCV infection. Fatigue associated with IFN therapy is almost universal, but rarely incapacitating. Etiology is multifactorial, and is related to the underlying disease, anemia, depression, insomnia, and the IFN itself. Fatigue can interfere with cognition and physical activities of daily living.² Interestingly, fatigue is more common in HCV infection than in liver diseases of other etiologies.³ There are tools designed to quantify fatigue, including the Fatigue Severity Scale (FSS), Fatigue Impact Scale (FIS), and the Fatigue Assessment Instrument (FAI).⁴⁻⁶ The latter has not been validated for HCV infection, and the FSS is the simplest to use. Patient expectations are important in dealing with fatigue, and all patients should be told to anticipate it (Table 2.1, see page 12). Fatigue is generally present throughout therapy, but it sometimes worsens in the latter stages of a 1-year treatment course. The treatment of fatigue is a challenge and, to date, no completely satisfactory therapy exists. Methylphenidate has been used by some clinicians, but with less than satisfactory results. A more useful pharmacologic therapy is modafinil, which works through promoting wakefulness and locomotor activity, although the exact mechanism is not known. Side effects include anxiety and nervousness, and insomnia may be exacerbated.

Insomnia is an important associated complaint, and ensuring a good night’s sleep is paramount. Patients often feel that napping is necessary, but in fact, those that have regular exercise patterns have improved sleep hygiene.⁷ Hypnotics are often necessary, at least periodically, for sleep (Table 2.1, see page 12).

Psychiatric Side Effects

Depression is common in Western society, more common in hepatitis C patients, and more common
still in IFN-treated individuals. The overall incidence of new depression is 20% to 30% during IFN therapy. This is again a class effect of the drug, and no IFN is free of this adverse event. There have been no well-designed studies to date to assess depression in clinical studies of HCV-infected patients. In both major registration trials for PEG IFN alfa-2a and alfa-2b, the assessment of depression was done through subjective clinician assessment. There may be perceived or cultural differences in depression rates, so subjective assessment is not accurate. Future studies must use validated assessment tools to truly determine the risk of depression while on therapy.

Although there have been isolated and rare cases of suicide and suicidal ideation on IFN therapy, depression is, for the most part, mild and controllable. The exact mechanism of how IFN leads to affective disorders is not fully clear, but a leading theory is that plasma tryptophan depletion leads to lower substrate levels for serotonin production in the brain, which results in depression. Depression onset is typically beyond the first month of therapy, and can occur at any time throughout therapy. Irritability and anxiety are common signs of depression and may be the only manifestations, especially in men. These should generally be treated in the context of treating the depression.

It is prudent to assess for depression prior to starting therapy with a thorough history of past events, as well as a validated scale, such as the Beck Depression Inventory (BDI-II) or the Center for Epidemiologic Studies-Depressed Mood Scale (CES-D). Periodic assessment with these scales throughout the course of therapy is useful in identifying some individuals with significant depression that may otherwise be missed. Pre-existing depression or even a remote history of depression that was moderate to severe may require a period of pre-emptive therapy (2–3 months is adequate) with an antidepressant prior to instituting IFN. Antidepressant use is required in roughly half of all patients, and the clinician should be familiar with at least two medications and have psychiatric consultation available if needed. The selective serotonin reuptake inhibitors (SSRIs) are well tolerated, widely used, and effective. They are occasionally not tolerated due to anxiety and motor agitation, but overall are a good first-line option. Examples of drugs in this class are escitalopram, citalopram, and sertraline. As a second-line option, the tricyclic antidepressants (TCAs) are a good choice. Adverse events include anticholinergic effects and weight gain.

One notable psychiatric disorder that is very difficult to treat is mania, or bipolar disorder. Mania is rare, but requires immediate drug discontinuation and urgent psychiatric assessment. Recently, cell-mediated disorders of immunity have been found in patients with bipolar disorder, raising the intriguing possibility of a direct link between immune modulation and exacerbation of mania. Interestingly, further evidence that the immune system is affected in neuropsychiatric disorders is that patients with schizophrenia have been found to have abnormal baseline cytokine profiles. Stable patients with schizophrenia can be safely treated with very close psychiatric follow-up (Table 2.2, see page 13).

### Thyroid Disorders

Hypothyroidism and, less commonly, hyperthyroidism occur in up to 12% of patients undergoing IFN therapy. Women are more commonly affected. These disorders can occur at any point throughout therapy, necessitating regular monitoring, but can also persist after discontinuation of IFN and may indeed be permanent.

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**Table 2.1. Constitutional Symptoms.**

<table>
<thead>
<tr>
<th>Problem</th>
<th>Diagnostics</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches/myalgias/arthralgias/fever</td>
<td>Check serum cryoglobulins if signs of vasculitis are present</td>
<td>Hydration</td>
<td>These are all common side effects, but be aware of the rare case of lupus or rheumatoid arthritis exacerbation</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Consider depression Assess for anemia, iron deficiency, and thyroid disorder</td>
<td>Antidepressant if indicated Treat anemia if present Modafinil 100–200 mg/d</td>
<td>Common side effect; severe cases may respond to modafinil daily or as needed</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Assess for depression/anxiety</td>
<td>Avoid nappingDecrease caffeine intakeExercise routinely</td>
<td>Insomnia can lead to worsening fatigue, and should always be addressed and treated</td>
</tr>
</tbody>
</table>

Rule out early encephalopathy in patients with cirrhosis

**Table 2.2.**
In a series of prospectively studied patients undergoing therapy with IFN and RBV, 11.8% (30/254) had biochemical thyroid dysfunction, with 8% having hypothyroidism and 4% having hyperthyroidism. There was no relationship with dose of IFN or response to therapy.\(^1\)

Thyroid antibodies can be found in one fifth of women infected with hepatitis C.\(^2\) Those with antibodies are more likely to develop overt thyroid disease on IFN than those without antibodies. However, there is little utility in screening for antibody, since it would not alter therapy or monitoring. Hypothyroidism during therapy should be treated with thyroid replacement, whereas hyperthyroidism should be evaluated promptly by an endocrinologist. The majority of affected patients are able to continue IFN therapy.

**Alopecia and Other Dermatologic Side Effects**

There are many skin disorders associated with hepatitis C itself, including cryoglobulin-associated vasculitis, porphyria cutanea tarda, cutaneous and/or mucosal lichen planus, and, rarely, salivary gland lesions, characterized by lymphocytic capillaritis, often resulting in extremely dry mouth.\(^3\) These lesions often improve with IFN therapy.

Dry skin is a frequent complaint related to IFN use. Psoriasis universally worsens with IFN but improves with discontinuation. Local therapies are generally ineffective, and short of stopping IFN, little else seems to help. The most commonly seen RBV-associated dermatologic complication is a macular rash, often quite pruritic and annoying to patients. The local administration of a corticosteroid cream is sometimes helpful, but RBV dose reduction is often required. Dose escalation can then be attempted once the rash improves. Patients should be instructed to use hypoallergenic soaps and lotions, and to avoid tanning and vigorous drying with towels.

Injection site reactions occur frequently, typically resulting in mild erythema at the site. This is transient, and cellulitis results only from poor sterilization techniques. Cool compresses applied to the site of injection can alleviate the discomfort associated with injection. The site of injection should rotate, with the abdomen being the preferred site due to the relatively large amount of subcutaneous fat present.

Alopecia occurs in up to one third of patients,\(^9\) but is usually seen in women with long hair. Some thinning of the hair is common in almost everyone on therapy. Patients need reassurance that alopecia is reversible once IFN is discontinued. Blow-drying of hair, peroxide-based permanents, and hair coloring should be avoided while on IFN therapy if hair loss is a problem. Vigorous brushing is not recommended, and only mild shampoos should be used.

**Ophthalmologic Side Effects**

Although ophthalmologic-related complications have been reported with IFN therapy, serious adverse events

### Table 2.2. Affective Disorders.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Diagnostics</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Mild to moderate depression | Assess routinely before and throughout therapy Clinical evaluation and standardized depression tool are best approaches | Institute SSRI antidepressant or dose escalate/add 2nd agent  
Pharmacotherapy examples:  
Escitalopram 10 mg/d  
Citalopram 20–60 mg/d | If suboptimal response to dose escalation, add 2nd agent or refer for psychiatric assessment |
| Severe depression        | Suicidal ideation or intent, diagnosed clinically or using depression index | Discontinue IFN/RBV and refer for urgent psychiatric evaluation—hospitalize if necessary | Most with severe depression will not be able to continue or resume therapy. This degree of depression is rare, but considered a medical emergency |
| Mania/ bipolar disorder  | Clinical diagnosis Any history of mania confirms diagnosis  | Discontinue IFN/RBV and refer for urgent psychiatric evaluation | Mania induced by IFN therapy can lead to significant morbidity. Most individuals will not be able to resume IFN |
| Schizophrenia            | Previously diagnosed and stable schizophrenia can be treated. Close psychiatric monitoring is essential throughout therapy on weekly to bimonthly basis | A stable regimen of psychotropic medications is necessary prior to IFN therapy. Changes in symptoms while on therapy need to be evaluated on a case-by-case basis | Stable patients with schizophrenia may tolerate therapy well, but require very close follow-up |
are extraordinarily rare. Most changes are retinal, mild, and transient, disappearing while the patient is still on therapy.\textsuperscript{16} Significant retinal hemorrhages and detachments, and vision loss are not typical. Retinal artery or vein thrombosis, or frank vision loss, has been noted in only a few cases.

While the prescribing information sheet recommends a baseline eye examination, this has not been adopted into widespread clinical practice. It does seem prudent, however, to screen patients with diabetes, patients with long-standing hypertension, and anyone with visual complaints. In those without any risk factors or complaints, an eye examination performed within the past 2 years is reasonable prior to initiating therapy.

Worsening diabetic retinopathy on IFN therapy has been reported, but the clinical significance is not known. In most cases, therapy can safely be continued with regular surveillance.\textsuperscript{17}

\section*{Pulmonary Side Effects}

Dyspnea with exertion associated with anemia is not uncommon. Dyspnea at rest not related to anemia has been noted with IFN and RBV therapy. The exact etiology is not clear, but progressive or severe dyspnea in rare cases may necessitate drug discontinuation.

A dry cough occurs infrequently with IFN monotherapy, but in roughly one fifth of those on combination therapy with RBV. The exact etiology of this is not well understood, but cough does improve with RBV dose reduction and abates with discontinuation. Over-the-counter cough remedies are also useful and should be first-line treatments.

Very rarely, more severe pulmonary complications have been reported to occur, including interstitial pneumonitis, pulmonary infiltrates, and worsening sarcoidosis, resulting in respiratory failure.\textsuperscript{18,19}

\section*{Gastrointestinal Side Effects}

Mild gastrointestinal complaints occur in the majority of patients in large trials with PEG IFN.\textsuperscript{8,9} Most commonly noted are anorexia, nausea, and diarrhea. Persistent vomiting is rare, and bloody diarrhea is not seen. Supportive measures, including adequate hydration and over-the-counter antiemetics or antidiarrhea medications, are generally adequate to treat these symptoms, though occasional dose reduction is necessary if symptoms are severe. For significant nausea or vomiting, pharmacologic therapy with ondansetron is generally effective.

\section*{Cardiovascular Side Effects}

Direct cardiac toxicity and arrhythmias are not known side effects of IFN or RBV. These complications have occurred during treatment, however, and are likely due to anemia brought on by combination therapy, with unmasking of underlying cardiac disease.

It is clinically appropriate to screen high-risk individuals for ischemic heart disease prior to therapy using one of several modalities of stress testing. In patients with significant cardiac disease associated with a high risk of short-term morbidity or mortality, IFN therapy is not indicated. In those with moderate cardiac disease who are eligible for therapy, it is important to prevent anemia using growth factors and modified doses of RBV.

\section*{Summary}

While adverse events are common with PEG IFN and RBV, they are rarely severe. The key to successful management lies in patient awareness and education prior to initiating therapy, as well as judicious use of antidepressants and other adjuvant therapies to treat side effects that do occur. Through careful monitoring of laboratory data and patient complaints, most patients will be able to complete a full course of therapy. The future of HCV therapy will likely be more complex with multidrug regimens; hence, side effect management will always play a major role in the care of the HCV-infected patient.
REFERENCES


Key Points

- Adherence to the optimal regimen of antiviral therapy for chronic hepatitis C virus (HCV) infection is important for achieving sustained virologic response (SVR).
- Side effects of antiviral therapy negatively affect adherence to the treatment regimen.
- Hematologic side effects are frequent causes of dose reduction or treatment discontinuation.
- Anemia related to peginterferon/ribavirin combination therapy negatively influences patients’ health-related quality of life (HRQL) and their adherence to the full dose of ribavirin.
- Hematopoietic growth factors, such as darbepoetin alfa and epoetin alfa, effectively treat anemia, improve patients’ HRQL, and help maintain a therapeutic dose of ribavirin.
- The clinical implications of neutropenia and thrombocytopenia are not clearly defined, and treatment with growth factor support is less well established.

In the past 5 years, it has been shown that SVR to the best available treatments for chronic HCV infection depends on adherence to the optimal dose and duration of peginterferon/ribavirin therapy. Patients who receive at least 80% of the dose of both drugs for at least 80% of the time have the highest SVR rates. The issue of adherence is especially important for patients infected with HCV genotype 1. Adherence to the optimal regimen seems to be especially critical during the first 12 weeks of therapy. Furthermore, the recent Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial—which evaluated retreatment of HCV-infected patients with advanced fibrosis who were nonresponders to previous treatment—suggests that it is important to deliver the optimal ribavirin dose during the first 20 weeks of therapy. Although dose reduction has a negative impact on SVR, treatment discontinuation is associated with the lowest rates of response. Several factors can either enhance or diminish adherence, but treatment of side effects is the most important determinant of dose reduction or discontinuation.

Hematologic side effects of combination therapy— anemia (23%), neutropenia (19%–24%), and thrombocytopenia (3%)—are frequent indications for dose reduction and therapy discontinuation. Dose reduction and discontinuation can successfully treat these side effects, but may reduce the likelihood of SVR. Hematopoietic growth factors have recently been assessed in an effort to avoid dose reduction or treatment discontinuation.

Anemia

Anemia is an important side effect of peginterferon/ribavirin combination. Generally, hemoglobin (Hgb) drop occurs within the first 1 to 2 months of therapy, subsequently stabilizing and returning to baseline value after treatment is discontinued. Anemia is an important cause for dose reduction or discontinuation. In fact, treatment-related anemia has been shown to be the main reason for discontinuation in 36% of all patients who stop antiviral therapy for chronic hepatitis C. Mild anemia (Hgb < 12 g/dL) is observed in nearly 50% of patients on interferon/ribavirin combination therapy. More profound anemia (Hgb < 10 g/dL) is observed in 9% to 13% of treated patients. The mean decrease in Hgb can be as high as 3.7 g/dL with pegylated interferon in combination with ribavirin.

Mechanism of Anemia

Several mechanisms contribute to development of anemia, and increasing evidence suggests “mixed anemia” related to combination therapy. Ribavirin causes a dose-dependent, reversible, hemolytic anemia. After entering red blood cells (RBCs) via a nucleoside transporter, ribavirin is activated by phosphorylation. Its subsequent accumulation within RBCs leads to adenosine triphosphate depletion, impairing the antioxidant mechanisms and contributing to the oxidative damage to RBC membranes. Extravascular removal of these cells by the reticuloendothelial system is followed by a drop in Hgb.

In addition to ribavirin-induced hemolytic anemia, interferons contribute to anemia by suppressing the bone marrow. It seems that interferon alfa monotherapy can cause a 0.5 g/dL reduction in Hgb. In a recently published study, compensatory reticulocytosis in response to ribavirin-induced hemolytic anemia was measured during ribavirin monotherapy as well as interferon alfa and ribavirin combination therapy. Although adequate reticulocytosis was noted in response to ribavirin-induced hemolytic anemia, this compensatory reticulocytosis was suppressed by interferon alfa,
suggesting that the bone marrow suppressive effect of interferon alfa contributes to the anemia associated with combination therapy.\textsuperscript{16}

**Consequences of Anemia**

Anemia induced by combination therapy is the main determinant of fatigue and can negatively influence HRQL.\textsuperscript{12-14} Although anemia affects several domains of HRQL (See Fig. 3.1), those related to occupational functioning, vitality, social functioning, and mental health are most profoundly impaired.\textsuperscript{13,17} It is important to remember that several factors besides anemia affect HRQL in patients with hepatitis C, including the flulike syndrome and neuropsychiatric side effects of interferon. Several studies have shown that HRQL declines early after antiviral therapy and rebounds shortly after antiviral therapy is discontinued.\textsuperscript{14} HRQL improvements over baseline scores have been demonstrated in patients who achieve SVR.\textsuperscript{14} Given the profound impact of combination antiviral therapy on HRQL, maneuvers to enhance quality of life should help patients tolerate the treatment and enhance adherence to the optimal dosing regimen.\textsuperscript{14}

Another unfortunate consequence of anemia is the need for dose reduction. Although quite effective in managing the anemia, ribavirin dose reduction can negatively impact virologic response and reduce the potential for an SVR or cure.\textsuperscript{1}

**Anemia Management**

Since approval of interferon alfa and ribavirin combination for treatment of chronic hepatitis C, management of the associated anemia has been increasingly emphasized. In general, management of anemia related to combination therapy involves ribavirin dose reduction or permanent discontinuation, per the manufacturer’s guidelines.\textsuperscript{7,14,15} These recommendations indicate to reduce the ribavirin dose when the Hgb level reaches 8.5 to 10 g/dL, and permanently discontinue treatment when Hgb \(\leq 8.5\) g/dL. The recommendations are stricter for patients with a history of stable cardiac disease.\textsuperscript{7,14,15}

A suggested alternative to dose reduction is the use of hematopoietic growth factors.\textsuperscript{7,11-14,19} Recombinant gene technology brought new management options for treatment of anemia with development of recombinant human erythropoietin (rHuEPO), epoetin alfa and beta, and recently, darbepoeitin alfa. Both darbepoeitin alfa and epoetin alfa are synthetic glycoproteins. Similar to endogenous erythropoietin (EPO)—a hormone produced by the cells lining the peritubular capillaries in the kidneys—darbepoeitin alfa and epoetin alfa stimulate erythropoiesis in the bone marrow. Enhanced erythropoiesis increases RBC count as well as Hgb and hematocrit levels.\textsuperscript{20,21}

Although both agents have similar tertiary protein configuration, darbepoeitin alfa has increased sialic acid content,\textsuperscript{20} which does not interfere with the receptor binding sites, but delays the clearance of darbepoeitin alfa, increasing its biologic activity. It has been shown that the half-life of endogenous EPO and rHuEPO is approximately 6 to 8 hours. The half-life of darbepoeitin alfa administered intravenously or subcutaneously is two- to threefold longer than rHuEPO. The longer half-life, which is attributed to the additional sialic acid-containing oligosaccharide side chains in darbepoeitin alfa, increases in vivo activity. Animal studies and clinical trials involving oncology and dialysis patients confirm the equivalency of weekly rHuEPO and biweekly darbepoeitin alfa. Together, these findings indicate that the properties of darbepoeitin alfa allow less frequent administration while preserving efficacy and safety.\textsuperscript{20-24}

**rHuEPO Treatment for Ribavirin-Induced Anemia**

rHuEPO has been increasingly used as a safe adjunct for managing anemia related to a variety of clinical scenarios including cancer chemotherapy, chronic renal failure, and as preparation for surgical procedures to minimize blood transfusions.\textsuperscript{21-24} Recently, two studies have reported the efficacy of rHuEPO in treating anemia related to the use of peginterferon alfa and ribavirin.\textsuperscript{12,13} The first involved 64 patients with chronic HCV infection who developed anemia (Hgb \(\leq 12\) g/dL) while receiving an antiviral regimen containing thrice-weekly interferon alfa and ribavirin. Anemic patients were randomized to either rHuEPO therapy (40,000 U QW SC) or standard-of-care (dose reduction, permanent discontinuation, or blood transfusions). A significant (\(P < .0001\)) increase in Hgb was noted in the rHuEPO arm (increase in Hgb +2.8 g/dL) as compared with standard-of-care anemia management (increase in Hgb +0.4 g/dL). In addition, a greater proportion of patients on rHuEPO (83%) maintained a ribavirin dose \(\geq 800\) mg/d than those managed through the standard-of-care approach (54%; \(P = .022\)).\textsuperscript{12}
A subsequent randomized, placebo-controlled trial assessed the safety and efficacy of epoetin alfa among anemic HCV-infected patients (Hgb ≤ 12 g/dL) receiving interferon alfa and ribavirin or peginterferon alfa and ribavirin.\textsuperscript{13} The protocol consisted of an 8-week double-blind phase (DBP) followed by an 8-week open-label phase (OLP). The results of this study confirmed the efficacy of epoetin alfa in treating combination-therapy–induced anemia and in maintaining the optimal ribavirin dose (maintained in 88% of patients on epoetin alfa versus 60% of patients on placebo; \textit{P} < .001). During the DBP, the increase in Hgb was higher for patients randomized to the epoetin alfa arm than those randomized to the placebo arm: The mean Hgb level at the end of the DBP was 13.0 ± 1.3 g/dL for the epoetin alfa group compared with 10.9 ± 1.1 g/dL for the placebo group (\textit{P} < .001). During the OLP, Hgb level was maintained in those who remained on epoetin and increased in those who switched from placebo to epoetin (See Fig. 3.2).\textsuperscript{13}

**Figure 3.2.**

Effect of Epoetin on Hgb Level.\textsuperscript{16}


In addition, a significant improvement in HRQL was noted for patients receiving epoetin alfa from randomization to the end of the DBP, as measured with the Medical Outcomes Survey Short Form-36 (SF-36) and the Linear Analog Scale Assessment (LASA). Although several scales in HRQL showed improvement, vitality and the role physical domain scores were most profoundly affected. Further analysis showed a stepwise increase in HRQL paralleling the gains in Hgb. The best improvement in HRQL scores occurred in patients who demonstrated an Hgb increase in of ≥2 g/dL. The same improvements in ribavirin dose maintenance, Hgb levels, and HRQL scores were observed in patients originally placed on placebo in the DBP who later received epoetin alfa during the open-label phase of the study. Although this study was not designed to show changes in SVR, an 8% increase in SVR in patients receiving epoetin alfa has been reported.\textsuperscript{19} This is encouraging, but limitations in the study design, the lack of adequate sample size to show a difference in SVR, and the absence of controls for potential confounders are potentially important drawbacks. Nevertheless, improvements in hematopoietic response, which can increase HRQL and help with treatment adherence, are quite valuable from both the patients’ and caregivers’ perspectives. This concept has been demonstrated for other chronic conditions, such as cancer chemotherapy; while adjunctive therapy does not necessarily have direct anticancer effects, it allows patients to tolerate treatment regimens associated with considerable side effects, thus improving their HRQL.\textsuperscript{13}

**Darbepoetin alfa Treatment for Ribavirin-Induced Anemia**

Darbepoetin alfa is a long-acting erythropoietic protein approved by the US Food and Drug Administration for treatment of anemia associated with chronic renal failure and cancer chemotherapy.\textsuperscript{20,21,26–28} As previously noted, darbepoetin alfa is a hyperglycosylated protein that makes it longer acting, thereby allowing less frequent dosing while maintaining the safety and efficacy of rHuEPO.\textsuperscript{20,21,26}

Two clinical trials have recently reported the safety and efficacy of darbepoetin alfa for the treatment of anemia in patients with chronic renal disease requiring dialysis.\textsuperscript{23,24} In one study, patients receiving epoetin alfa were randomized into two groups. The first group continued with their epoetin three times weekly but the other group was changed to weekly darbepoetin alfa.\textsuperscript{21} In a second study, patients with renal failure on dialysis who were receiving stable doses of rHuEPO were randomized into two groups. The first group continued to receive rHuEPO at their current regimen while the other group was changed to an equivalent dose of darbepoetin alfa at a reduced frequency.\textsuperscript{24} The data from these studies suggested that darbepoetin alfa administered at a reduced frequency was as safe and effective as epoetin for the treatment of anemia among dialysis-dependent patients with chronic renal disease.\textsuperscript{23,24}

Two additional studies using darbepoetin alfa have been reported for treatment of anemia related to cancer chemotherapy.\textsuperscript{27,28} The first, a two-part study, was designed to assess the safety and feasibility of weekly and biweekly administration of darbepoetin alfa. The results suggested a safety profile for darbepoetin alfa similar to that for epoetin alfa. In addition, increasing doses of darbepoetin alfa resulted in increased efficacy and faster response rates.\textsuperscript{27,28}

A recent study investigated the use of darbepoetin alfa for management of anemia in HCV-infected patients.\textsuperscript{19} In this pilot study, 50 treatment-naive patients with
chronic hepatitis C were given peginterferon alfa-2b (1.5 µg/kg QW) and a weight-based ribavirin dose (800–1400 mg/d). Anemia occurred frequently during antiviral therapy. By treatment week 12, mild anemia (Hgb ≤ 12 g/dL) occurred in approximately 65% of patients, and severe anemia (Hgb ≤ 10.5 g/dL) occurred in approximately 25% of patients. Anemia had a negative impact on HRQL, especially the domains related to energy and activity. The protocol required patients with severe anemia (Hgb ≤ 10.5 g/dL) to begin darbepoetin alfa 3 µg/kg every other week to tightly maintain their Hgb level between 10.5 g/dL and 12 g/dL. Of 50 enrolled patients, 36% (18/50) received darbepoetin alfa. In preliminary analyses, darbepoetin alfa successfully maintained Hgb within the target range. After 8 weeks of darbepoetin alfa, 92% of patients maintained an optimal ribavirin dose (>10.6 mg/kg/d). In fact, their ribavirin dose was 12.4 mg/kg/d. Early analyses of these data also suggest improvement in HRQL scores and no serious adverse events attributable to darbepoetin alfa. The final analysis of this study, including HRQL analysis, virologic response, and safety data, is forthcoming.

**Figure 3.3.**

**Darbepoetin alfa Successfully Maintains Hgb Within the Target Range.**

The clinical implications of neutropenia in the setting of anti-HCV treatment are controversial. First, it has been suggested that, unlike cancer chemotherapy-induced neutropenia, interferon-related neutropenia is not necessarily associated with an increased risk for major bacterial infections. Bacterial infections can occur in 2% to 4% of patients on standard or pegylated interferon. It seems that serious bacterial infections are rarely associated with interferon-related neutropenia (ANC [absolute neutrophil count] = 500–999/mm³). In one recently published study involving 119 patients treated with peginterferon/ribavirin, there was no relationship between the severity of neutropenia and bacterial infection in 22 patients who developed neutropenia. Additional research is needed to further elucidate the clinical implication of interferon-induced neutropenia and its associated risk for infections.

**Neutropenia Management**

In general, patients who develop neutropenia are managed with dose reduction or permanent interferon discontinuation as per guidelines provided in package inserts. For patients on peginterferon alfa-2b, a 50% dose reduction is recommended when the ANC falls below 750/mm³, and the drug is permanently discontinued when the ANC falls below 500/mm³. For peginterferon alfa-2a, the dose is reduced to 135 mg when the ANC falls below 750/mm³ and stopped when the ANC falls below 500/mm³. As with anemia, it may be possible to treat neutropenia and prevent interferon dose reduction with growth factors. Clinicians who use this strategy commonly consider growth factors for patients with significant neutropenia.

Growth factors have been used extensively to treat neutropenia related to several conditions, including cancer chemotherapy. Genetic engineering technology has made it possible to produce recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF) or filgrastim and its covalent conjugate, pegfilgrastim. Filgrastim is structurally similar to the G-CSF produced by human cells except for an additional methionine at the N-terminal of the protein chain that allows its expression in *Escherichia coli*. The difference between the two products is that filgrastim is a nonglycosylated molecule, weighing approximately 19 kD, whereas pegfilgrastim is produced by covalently binding a 20 kD glycol molecule to the N-terminal methionyl residue of filgrastim. The half-

returns to baseline after treatment discontinuation. Although neutropenia can be seen with both thrice-weekly interferon and pegylated interferon alfa, the degree of neutropenia is more profound with pegylated interferon.
Thrombocytopenia

Thrombocytopenia is sometimes observed in patients receiving interferon-based treatment regimens and may be more profound with the pegylated interferons. The severity of thrombocytopenia is usually related to the baseline platelet count and the presence of cirrhosis and portal hypertension. The use of ribavirin in combination with interferon may blunt the thrombocytopenic effect of interferons as a result of reactive thrombocytosis. The decrease in platelet count is primarily due to reversible bone marrow suppression, although autoimmune thrombocytopenia can rarely occur. With pegylated interferons, the platelet count decreases gradually over 8 weeks and stabilizes thereafter, returning to baseline.

Consequences of Thrombocytopenia

The impact of interferon dose reduction due to thrombocytopenia on SVR has not been established. Because bleeding has not been observed in HCV-infected patients with low platelet counts (<50,000/mm³), interferon discontinuation or dose modification is rarely necessary. In fact, severe thrombocytopenia was the reason for treatment discontinuation in <1% of patients treated in trials of peginterferon/ribavirin.

Thrombocytopenia Management

Package inserts of antiviral therapies recommend dose reduction based on established guidelines. That is, a 50% dose reduction is recommended for platelets <80,000/mm³ during treatment with peginterferon alfa-2b or for platelets <50,000/mm³ during treatment with peginterferon alfa-2a, and permanent treatment discontinuation is recommended for platelets <50,000/mm³ or <25,000/mm³ for these two treatments, respectively.

Several studies have explored strategies to stimulate megakaryocyte production and maturation in the bone marrow mediated by cytokines or growth factors. Oprelvekin is a recombinant human interleukin-11 that acts as a thrombopoietic growth factor. The US Food and Drug Administration approved it for oncologic adjunct therapy in the management of thrombocytopenia. The potential safety and efficacy of oprelvekin was evaluated in an open-label study of 13 patients with chronic hepatitis C treated with standard interferon alfa-2b (3 MU TIW) and ribavirin (1000–1200 mg/d). Oprelvekin was given simultaneously at a subcaneous dose of 50 μg/kg TIW. Oprelvekin treatment resulted in higher mean platelet count at 2 weeks than baseline (98,600/mm³ versus 73,600/mm³, P < .05). An important side effect of this treatment was fluid retention, which was noted in all patients, and 77% requiring diuretic therapy. The side effect profile of oprelvekin in patients with HCV-related cirrhosis makes its use problematic. Currently, there is little enthusiasm for its use. Newer growth factors for treatment of thrombocytopenia with more favorable safety and efficacy profiles are currently in development.

Summary

Hematologic side effects represent a fundamental dilemma for hepatologists, gastroenterologists, infectious disease specialists and physician extenders treating patients with HCV infection. These side effects, particularly anemia, can negatively influence patients’ HRQL, compromising their adherence to the optimal regimen. Reducing the dose of combination therapy to relieve hematologic side effects is usually effective but can result in suboptimal doses of anti-HCV therapy and may negatively impact SVR. The use of hematopoietic growth factors provides an alternative to dose reduction and helps maintain patients’ HRQL. Although preliminary data concerning the use of growth factors for hematologic side effects such as anemia are quite exciting, growth factor use for treatment of thrombocytopenia is fraught with its own potential side effects. As hepatitis C treatment advances, it will be important to optimize adherence to the recommended treatment as well as patients’ HRQL. It may be that adjunctive therapies and support with growth factors will allow patients to tolerate the optimal antiviral dose while improving or maintaining their well-being.
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IV.

MANAGEMENT OF TREATMENT-RESISTANT PATIENTS WITH HEPATITIS C

Ira M. Jacobson, MD

Key Points

- Nonresponders to interferon/ribavirin (IFN/RBV) can be treated with peginterferon (PEG IFN)/RBV, with a small but real chance of success (overall sustained virologic response [SVR] approximately 10%), while relapsers fare better (SVR approximately 50%).
- There is no standard approach to PEG IFN/RBV nonresponders, but a longer course of PEG IFN/RBV in prior relapsers may be considered. Investigational alternatives include daily consensus interferon (CIFN)/RBV, daily CIFN/IFN-gamma, and novel agents.
- Maintenance therapy is an investigational application of PEG IFN for patients who fail to reach SVR to PEG IFN/RBV, and may be considered in patients with advanced fibrosis.

With each advance in the evolution of antiviral therapy for chronic hepatitis C, patients who have failed to respond to previous therapy have been evaluated for response to the most recently introduced treatment. Thus, in the era prior to combination therapy, patients who had relapsed or failed to respond to 6 months of IFN monotherapy were re-treated with IFN for a longer duration with modest success in relapsers, but minimal success in nonresponders. Subsequently, patients who had failed treatment with IFN monotherapy were treated with combination therapy consisting of IFN and RBV. These studies established an SVR rate of 50% to combination therapy in prior IFN relapsers and, in meta-analyses of a number of studies, 13% to 15% of prior nonresponders to IFN.

In some studies, prolonged duration of retreatment with combination therapy from 6 to 12 months in IFN monotherapy relapsers appeared to be beneficial, particularly in patients infected with hepatitis C virus (HCV) genotype 1. By implication, prolonged therapy may be necessary to complete the process of clearance of infected hepatocytes in some patients long after serum clearance has been achieved. This is consistent with the prevailing concept of a biphasic pattern of response in which the first phase represents inhibition of viral production, while the second, much more prolonged phase, represents predominantly the loss of infected hepatocytes, presumably via an immunologic response, as a critical determinant of successful treatment. The concept of prolonged therapy beyond the standard 48 weeks in patients with a high risk of relapse, such as delayed responders, remains of interest in the current era of PEG IFN and RBV.

Since the superior efficacy of PEG IFN over standard IFN, either alone or with RBV, was established in treatment-naive patients, trials evaluating the efficacy of PEG IFN and RBV in nonresponders to IFN with or without RBV have been completed, with one trial published and others awaiting publication. Although characterized by considerable heterogeneity in design with regard to doses of PEG IFN and RBV, there has been substantial consistency in outcomes.

Trials of PEG IFN/RBV in IFN/RBV Treatment Failures

We recently reported a completed trial of PEG IFN alfa-2b and RBV in combination therapy nonresponders, relapsers, and IFN monotherapy nonresponders. There were two treatment arms: PEG IFN alfa-2b 1.0 µg/kg with RBV 1000 to 1200 mg (regimen A) and PEG IFN alfa-2b 1.5 µg/kg with RBV 800 mg (regimen B). The rationale for the reduced RBV dose in the second treatment arm was that this dose was being evaluated in the contemporaneous pivotal trial of Manns et al. SVR rates are shown in Table 4.1. None of the differences between the two regimens was statistically significant.

### Table 4.1.

<p>| SVR Rates with PEG IFN alfa-2b 1.0 µg/kg + RBV 1000–1200 mg (Regimen A) and PEG IFN alfa-2b 1.5 µg/kg + RBV 800 mg (Regimen B) in Prior Nonresponders and Relapsers. |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>SVR to Regimen A</th>
<th>SVR to Regimen B</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN monotherapy nonresponders</td>
<td>16%</td>
</tr>
<tr>
<td>IFN/RBV nonresponders</td>
<td>6%</td>
</tr>
<tr>
<td>IFN/RBV relapsers</td>
<td>32%</td>
</tr>
</tbody>
</table>

When all of the groups were pooled together, the end-of-treatment response rate was approximately twice the SVR rate, signifying a relapse rate in treatment responders of 50%, and even higher in the prior combination therapy nonresponders. Such relapse rates are far higher than those reported in studies of
treatment-naive patients given PEG IFN/RBV.14,15 It is possible that a more prolonged course of therapy (eg, 18–24 months) might be useful in some IFN/RBV combination therapy nonresponders or relapers who become HCV RNA negative by polymerase chain reaction (PCR) during a subsequent course of PEG IFN/RBV.

Across all groups in this study, patients with advanced fibrosis (F3–4) had similar rates of SVR compared with patients having mild fibrosis (F0–2; 15% versus 16%). However, in patients with F3–4, SVR was significantly greater in those receiving the higher rather than the lower dose of PEG IFN (24% versus 5%; P = .003). There was no such difference among patients with F0–2. This suggests that higher doses of PEG IFN are particularly important in patients with more advanced fibrosis. Other findings included poor response rates among African Americans, as demonstrated previously.16,18,20

Patients with normal alanine aminotransferase (ALT) levels at entry had an overall SVR rate of 21% compared with 14% in those with high ALT levels, underscoring the evolving consensus that normal ALT levels should not preclude consideration of HCV therapy. Finally, prior nonresponders to combination therapy had a fourfold increase in SVR if the HCV RNA level at the end of prior therapy was <100,000 copies/ml compared with those whose levels exceeded this figure (5% versus 21%).

Similar conclusions have been reached by other investigators evaluating PEG IFN alfa-2b in prior nonresponders. Lawitz et al21 found an SVR of 10% in combination nonresponders given PEG IFN alfa-2b 1.5 µg/kg and RBV 1000–1200 mg for 12 weeks followed by PEG IFN alfa-2b 1.0 µg/kg and RBV 800 mg for 36 weeks. In prior combination therapy relapers on this regimen, the SVR was 37%. Combination therapy nonresponders who had a drop in HCV RNA >1 log with prior therapy had a 24% rate of SVR in this trial, compared with only 5% in those with a <1-log drop with prior combination therapy.21

Somewhat higher SVR rates were found in a study by Krawitt et al,22 wherein combination therapy nonresponders had an SVR of 20% (17% in genotype 1), while prior combination therapy relapers had an SVR of 54%. A trial by Freilich et al23 reported preliminarily no advantage of adding amantadine to PEG IFN/RBV in prior nonresponders and relapers.

The Hepatitis C Long-term Treatment Against Cirrhosis (HALT-C) study, sponsored by the National Institutes of Health, is a multicenter trial of PEG IFN alfa-2a maintenance therapy at a dose of 90 µg/week in prior nonresponders to either IFN/RBV or IFN alone. Eligible patients had Ishak fibrosis scores of 3 to 6. The trial had a lead-in phase during which patients received PEG IFN alfa-2a 180 µg/wk and RBV 1000–1200 mg/d. Patients who cleared HCV RNA after 20 weeks of treatment were continued on combination therapy for a total of 48 weeks in the hope of obtaining an SVR, while those who remained viremic were randomized to long-term maintenance therapy for 4 years. SVR data in patients clearing HCV RNA after the first 20 weeks of combination therapy have been published recently.16

Of the first 604 patients enrolled in the HALT-C study, 34 (5.6%) withdrew from the trial before week 20. 360 patients (60%) had detectable HCV RNA in serum and were eligible for the maintenance phase, and 210 (35%) were HCV RNA negative at 20 weeks and remained on PEG IFN/RBV therapy for a total of 48 weeks. Eighteen patients developed virologic breakthrough, 192 (32%) were PCR negative at the end of therapy, and 109 (18%) achieved SVR. Those patients with previous nonresponse to IFN alone had an SVR of 28%, compared with those with nonresponse to IFN/RBV (12%) (P < .0001).

The HALT-C trial confirmed data from prior studies in treatment-naive patients on the importance of adherence to dosing in achieving desired virologic outcomes.24–26 RBV dose reductions from >80% to <60% of the target dose during the first 20 weeks of treatment significantly reduced the week-20 virologic response, as did concurrent dose reductions of both PEG IFN and RBV; however, dose reductions of PEG IFN alone did not do so. In contrast, dose reductions instituted beyond the 20-week time point did not impair SVR. Consistent with other observations, African Americans fared poorly in this study. The data from the maintenance phase of this trial are not yet available.

A potential way to enhance response with retreatment would be to use a higher dose of PEG IFN. This hypothesis has been tested in the RENEW trial in which PEG IFN alfa-2b 3.0 µg/kg (twice the usual dose) and RBV 1000–1200 mg were compared with PEG IFN 1.5 µg/kg and RBV 1000–1200 mg. Gross et al27 preliminarily reported virologic clearance in 42% of the higher-dose PEG IFN recipients at 24 weeks compared with 30% in those receiving the standard dose. Preliminary analysis of SVR data, however, indicated no significant benefit of the higher dose, but final results have not yet been presented.27

Thus, studies indicate that previous nonresponders can respond to PEG IFN/RBV, with combination therapy nonresponders having a 10% overall chance of SVR. I consider patients for retreatment on the basis of several factors. The most important distinction to be made is whether the patient was a nonresponder or relaper, because relapers have a much better chance of achieving SVR. Thus, a greater degree of selectivity should apply to prior nonresponders than relapers. In combination therapy nonresponders, the degree of decline in viral load with previous therapy is a sufficiently important determinant of future response to PEG IFN/RBV that it is a reasonable consideration in the decision-making process with the patient. In addition, the degree of fibrosis is a critical element in
Alternative Strategies for Enhancing Response Rates in IFN/RBV

Nonresponders

There has been growing interest in the use of consensus interferon (IFN alfacon-1; CIFn) in combination therapy nonresponders following a recent study reporting that daily CIFn, given in two different high-dose induction regimens for 12 weeks, (Regimen 1: 18 μg CIFn QD for 4 weeks, followed by 9 μg CIFn QD for 8 weeks; Regimen 2: 27 μg CIFn QD for 4 weeks, followed by 18 μg CIFn QD for 8 weeks) and then CIFn 9 μg daily for 36 weeks, combined with RBV, induced SVR rates as high as 40% in nonresponders to IFN/RBV.9 Final reports on efficacy and tolerability in larger numbers of patients are awaited, but these data have led to interest in similar regimens for nonresponders to PEG IFN/RBV.9

A feature of the nonresponder studies presented to date is the higher relapse rate in patients who become HCV RNA negative on treatment compared with relapse rates in treatment-naive patients. Perhaps 48 weeks of therapy are not sufficient to eradicate all intrahepatic viral reservoirs, a process that is presumed to occur during the prolonged second phase of viral clearance. A tantalizing suggestion that 72 weeks of therapy may be superior in intrinsically resistant patients was presented recently by Buti et al., who demonstrated SVR in 7 out of 8 patients with late response (PCR positive at 12 weeks; negative at 24 weeks) treated with 72 weeks of PEG IFN and RBV. On a much larger scale, results from the TeraViC-4 study reported at the European Association for the Study of Liver Diseases 2004 annual meeting support the idea that patients who are slow to become PCR negative may benefit from longer-duration therapy.10 In this study, patients not becoming PCR negative at week 4 were randomized to receive an additional 44 weeks (n = 165) or 68 weeks (n = 162) of therapy with PEG IFN alfa-2a (180 μg QW) plus RBV (800 mg/ d). Patients receiving a total of 72 weeks of therapy had a significantly higher rate of SVR (46%) compared with those receiving only 48 weeks of therapy (32%; P = .0144). For patients with genotype 1, the SVR rates were 44% and 28%, respectively.

Although these were studies of treatment-naive patients with delayed response, it is tempting to extrapolate results to patients who were prior nonresponders because they, too, have high rates of relapse after becoming PCR negative on therapy. This raises consideration of prolongation of therapy beyond 48 weeks in prior nonresponders, particularly in patients with advanced fibrosis for whom the clinical consequences of treatment failure may occur sooner than in those with mild disease. The decision to prolong therapy beyond 48 weeks should consider each patient individually and take into account tolerance of therapy, the patient’s level of commitment, and the degree of fibrosis, as these help to determine how aggressively therapy should be pursued. When I do embark on a prolonged course of therapy, it is only after extensive discussions with the patient about the rationale and uncertainties, and the nonstandard, “off-label” nature of such prolonged therapy.

Approach to PEG IFN/RBV Treatment Failures: Are There Still Options for Curative Therapy?

The patients most tempting to re-treat with a repeat course of PEG IFN/RBV with curative intent are those who relapsed after becoming PCR negative for HCV RNA with prior therapy. Based upon the afore-cited experience in the 1990s with successful treatment of IFN relapsers using more prolonged courses of therapy, clinicians may wish to consider retreatment of genotype 1 patients who have relapsed after 12 months of PEG IFN and IFN with an 18- to 24-month course of therapy. Alternatively, patients infected with genotype 2 or 3, who often receive 6 months of therapy, might be re-treated for 12 months. Despite the foundation for this approach based upon our historic experience with IFN monotherapy relapers, no published trials bearing on this issue have been reported. In practice, some clinicians do currently offer their relapsing patients this option, particularly if the patient has advanced fibrosis and tolerated prior treatment acceptably.

Anecdotally, clinicians have tried “crossing over” to another PEG IFN after previous nonresponse to treatment, but at present there are no published studies indicating a potential for a course of one PEG IFN/RBV to result in SVR after failure to respond to a previous course of a different PEG IFN/RBV. Similarly, there is no evidence that a higher-than-standard dose of either PEG IFN or RBV can affect SVR in a previous nonresponder. If a patient has failed to have an early virologic response after 12 weeks of therapy, and there has been a major lapse in adherence to intended dosing or a prolonged treatment interruption, the clinician might wish to extend therapy for a longer time, if the clinician feels that adherence can be improved. This might arise, for example, if RBV interruption occurred because of severe anemia and erythropoietin was subsequently initiated, or if psychiatric side effects that necessitated dose interruption have been addressed and a collaborating psychiatrist feels that it is safe to continue or restart therapy.

Alternative treatment options for nonresponders to PEG IFN/RBV have yielded promising results in single-center studies. In a German trial, two regimens
of daily CIFN with RBV were compared: one with CIFN 27 μg/d for 4 weeks, 18 μg/d for 12 weeks, followed by 9 μg/d for weeks 50–72 (depending upon when HCV RNA clearance occurred), and the other with a CIFN dose of 9 μg/d for 50 to 72 weeks, each combined with RBV. SVR occurred in about 25% of previous nonresponders to PEG IFN/RBV.29 The 9-μg daily regimen was not significantly less effective than the induction regimen. Provocative data have recently emerged utilizing a combination of CIFN and IFN-gamma. The foundation for this regimen was the observation of in vitro synergistic suppression of genomic replication in flavivirus and HCV replicon systems exposed to both CIFN and IFN-gamma. In a small pilot study, this combination was reported to produce a 24-week treatment response in 65% of prior nonresponders to PEG IFN/RBV.30 Both of these combination treatments are currently being evaluated in multicenter studies of nonresponders; however, it is too early to make recommendations about use outside of clinical trials.

Trials of other novel agents in combination therapy nonresponders are being initiated or are currently anticipated. These include an antisense drug, polymerase inhibitors, an inosine monophosphate dehydrogenase inhibitor (IMPDH, an enzyme that catalyzes guanosine synthesis), and CpG oligonucleotides, which stimulate plasmacytoid dendritic cells and B cells. Protease inhibitors are also in development. As with treatment-naive patients, however, it is important for patients to understand the likelihood that it will be years before novel agents are widely available for treatment of nonresponders.

**Approach to PEG IFN/RBV Treatment Failures: Prolonged or Maintenance Therapy?**

There is great interest in the use of IFN for its potential anti-inflammatory and antifibrotic effects for patients with advanced fibrosis in whom viral eradication cannot be achieved. These considerations apply somewhat more to nonresponders than to relapers after therapy with PEG IFN/RBV, in whom a repeat course of therapy of longer duration might be considered with curative intent. On the other hand, if the physician or patient is disinclined to attempt prolonged therapy, relapers with advanced fibrosis (F3–4) may be particularly good candidates for maintenance therapy because, among patients with prior treatment failure, they are likely to have the greatest reduction in viral level with retreatment. The degree of reduction in viral load appears to correlate with chance of histologic improvement.32,33 Several lines of evidence support the concept of a histologic benefit of IFN therapy. In vitro, IFN alfa inhibits the activation of stellate cells, the scar-producing cells of the liver. Many clinical studies of IFN, with or without RBV, show that some virologic nonresponders have significant reductions in hepatic activity indices (HAI).34-36 A recent comprehensive analysis of several historic trials indicates not only reduction in inflammation but also a trend toward improvement or stabilization of fibrosis, and even regression of fibrosis in some patients, after completion of therapy. These benefits were maximal in, but not limited to, sustained virologic responders.35 Moreover, several studies have suggested improved clinical outcomes over prolonged observation periods, including reductions in the risk of hepatocellular carcinoma (HCC) and other complications of cirrhosis, in patients treated with self-limited courses of IFN-based therapy37-40 compared with patients receiving no treatment. Studies from Japan further suggest a particular likelihood of reduced risk of HCC in patients without SVR but with sustained biochemical response.41-43 Since most of these observations have been made in the context of trials involving 6- to 12-month courses of therapy, cessation of therapy after only 12 weeks in virologic nonresponders may be premature, if the patient is to derive maximum histologic benefit from treatment.

Widespread interest in maintenance therapy has been fueled by a published randomized trial of maintenance therapy with IFN, in which patients with histologic improvement after 6 months of virologic nonresponse to IFN received either 24 additional months of IFN 3 MU TIW or no treatment. Treated patients had significantly lower HAI scores at the end of the treatment period and a trend toward less fibrosis.41 As discussed elsewhere in this publication (see “Lack of Sustained Response in Hepatitis C: Considering Maintenance Therapy”), three large multicenter studies currently in progress in prior nonresponders to IFN-containing regimens are evaluating the efficacy of lower doses of either PEG IFN than those used for treatment-naive patients (ie, PEG IFN alfa-2b 0.5 μg/kg or PEG IFN alfa-2a 90 μg). The Colchicine Versus PegIntron Long-term (COPilot) study is comparing PEG IFN alfa-2b 0.5 μg/kg QW with colchicine 0.6 μg twice daily for 4 years in patients with Ishak fibrosis scores of 3 to 6. A second study, Evaluation of PegIntron in Control of Hepatitis C Cirrhosis (EPIC), is evaluating PEG IFN alfa-2b 0.5 μg/kg QW versus no treatment for 3 years in patients with Metavir fibrosis scores of F2 and F3, and for 5 years in patients with F4. Patients receive an initial course of full-dose PEG IFN alfa-2b and RBV, and transition to the maintenance dose of PEG IFN without RBV, or no treatment after 12 weeks if HCV RNA has failed to clear. On the other hand, if patients clear HCV RNA, then full doses of PEG IFN and RBV are continued for 48 months. The third maintenance trial, HALT-C, compares PEG IFN alfa-2a 90 μg QW or no treatment for 4 years in patients with Ishak scores of 3 to 6. Although all of these trials are well...
intentioned with regard to the use of low doses of PEG IFN to enhance tolerability over a long period of treatment, it is possible that the use of reduced doses might also decrease the benefits that maintenance therapy could otherwise provide.

An interim analysis of the COPILOT study yielded interesting but inconclusive evidence on efficacy. The study is designed for 48 months of treatment, but interim data up to 24 months in 300 patients with cirrhosis revealed lower rates of variceal bleeding, liver failure, and liver transplantation in the PEG IFN-treated recipients than in the colchicine recipients. These data are very preliminary and cannot be taken to justify routine use of maintenance therapy in standard practice at this time.

Proponents of maintenance therapy vary in terms of which parameters encourage them to pursue this form of treatment. Some evidence favors a correlation between reduction in viral load and improvement in Histological Activity Index (HAI) scores in nonresponders to therapy, regardless of biochemical response. Based on his study on maintenance therapy, Shiffman believes that only patients with reductions in HCV RNA of >2 logs have significant histologic benefit. Other data suggest a correlation between HAI reduction and normalization of ALT. It is important to note that in the published trial of maintenance therapy with standard IFN, patients were enrolled only if they had interim improvement in HAI score after 6 months of treatment. Thus, an evidence-based approach would currently require repeat biopsy after 6 months to assess for HAI reduction as a means to select patients who are likely to benefit from maintenance therapy. This is unlikely to be widely adopted, however, because of patient disinclination to undergo repeated liver biopsies, and because it is not yet clear that the benefit of maintenance therapy is restricted only to patients with interim improvement on a repeat biopsy.

Many experts feel that long-term maintenance therapy in nonresponders to current treatment should be restricted to clinical trials. At the present time it seems reasonable to discuss with patients who have bridging fibrosis or cirrhosis, and who decline to participate in clinical trials, the option of long-term maintenance therapy with a reduced dose of PEG IFN. I am more inclined to offer maintenance therapy to patients who have achieved a substantial reduction (at least 1–2 logs) in viral load, particularly with reduction or normalization of ALT. An interim liver biopsy demonstrating improvement in histology is probably ideal, but patients are usually reluctant to undergo biopsy, and more importantly, it is not yet clear whether benefit, if it exists at all, will depend upon such interim improvement. The theoretic benefits and uncertainties of maintenance therapy, as well as the unproven and off-label nature of this approach, are discussed with the patient. Active clinical investigators or clinicians with access to such centers should inform patients that ongoing maintenance therapy will likely exclude a patient from being eligible for clinical trials of new treatments for HCV. Given the investigational nature of maintenance therapy, there is no standardized dose of PEG IFN for this application.

Whether RBV, alone or in combination with IFN, might be of benefit as maintenance therapy has been given far less attention. This may be related to the longer track record for IFN, the many studies suggesting interval improvement in inflammation in some nonresponders to IFN, the greater antiviral potency of IFN monotherapy than RBV monotherapy, and the anemia and teratogenicity inherent in RBV use, along with its capacity for mutagenicity in vitro. However, the results of a randomized study by Hoofnagle et al suggest that RBV should not be overlooked entirely. In this trial, nonresponders to a 24-week course of IFN/RBV combination therapy were randomized to receive 48 additional weeks of RBV monotherapy or placebo (n = 17 in each group). Consistent with earlier studies on RBV monotherapy, there was no effect on HCV RNA levels during the RBV maintenance phase, but mean ALT was significantly reduced. Even more compelling, RBV maintenance was associated with significant histologic improvement compared with placebo. Despite these intriguing results, the large-scale trials that would be necessary to firmly establish a role for RBV maintenance therapy are not currently being performed and few clinicians seem to use it.

Conclusions

Nonresponders to IFN/RBV can be treated with PEG IFN/RBV, with a small but real chance of success (overall SVR approximately 10%), while relapers fare better (SVR approximately 50%). There is no widely accepted approach to PEG IFN/RBV nonresponders, but a longer course of PEG IFN/RBV in prior relapers may be considered. In studies of PEG IFN/RBV, preliminary results have led to multicenter studies with daily CIFN/RBV or daily CIFN/IFN-gamma. Novel agents in combination with PEG IFN/RBV are also being evaluated. Maintenance therapy for patients who fail to reach SVR to PEG IFN/RBV is currently an investigational application of PEG IFN, with practitioners having the option of offering this to patients with advanced fibrosis. As is so often true in the management of HCV-infected patients, consideration of therapeutic options in nonresponders is labor-intensive, highly individualized, and dependent upon extensive discussions with patients, who must be active participants in the decision-making process.
REFERENCES


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Key Points

- Hepatic inflammation leads to fibrosis progression.
- Decline in hepatitis C virus (HCV) RNA level during interferon therapy is associated with an improvement in hepatic inflammation.
- Interferon maintenance therapy may be successful in preventing fibrosis progression and reducing the risk of hepatic decompensation in those patients where the serum HCV RNA level can be kept at a significantly reduced level when compared with the pretreatment baseline.
- Only those patients with advanced bridging fibrosis or stable cirrhosis should be considered for peginterferon maintenance therapy.
- The proper dose of peginterferon for maintenance therapy has yet to be defined.

Several years ago it was hypothesized that continuing interferon or peginterferon long-term over several years as maintenance therapy could benefit those patients who failed to achieve SVR. A single preliminary study of maintenance therapy, in which standard interferon monotherapy was administered three times weekly over 2 years, clearly demonstrated that such an approach could prevent fibrosis progression in a select group of nonresponders. This observation laid the foundation for conducting large, randomized, controlled trials of maintenance therapy in patients with chronic HCV infection who failed to achieve SVR following previous therapy with peginterferon/ribavirin. The Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial, sponsored by the National Institutes of Health, is the largest and most well recognized of these studies.

Relationship Between Virologic and Histologic Response

Histologic response is determined by comparing liver histology prior to and after completing a defined period of anti-HCV treatment. Although several definitions for histologic response have been utilized over the past decade, the one most commonly utilized has defined histologic response as a 2-point or greater decline in the inflammation score and/or a 1-point decline in fibrosis. In these studies, the second or follow-up liver biopsy was performed 24 weeks following the completion of interferon therapy. Whether or not this definition is clinically significant and whether this was actually the correct time point at which to obtain the repeat biopsy for histologic comparison has never been evaluated.

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<td>Achieve SVR and “cure”</td>
<td>Reduce serum HCV RNA level</td>
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<td>Reduce hepatic inflammation</td>
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<td>Reduce the severity of extrahepatic manifestations of HCV infection</td>
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No therapy, both the serum HCV RNA level and degree of hepatic inflammation.

Fibrosis may also improve in patients with chronic HCV infection following interferon therapy. There is now little doubt that patients who achieve SVR can have regression in fibrosis; this has been observed in nearly all studies in which patients who achieved SVR underwent repeat liver biopsy and both the pre- and posttreatment biopsies were compared. However, these same studies clearly demonstrate that patients with either relapse or nonresponse do not have any meaningful reduction in liver fibrosis following a single course of anti-HCV treatment, despite claims to the contrary. Unfortunately, those studies which have suggested that fibrosis and possibly even cirrhosis could regress in nonresponders have failed to account for sampling variation and emphasized only those patients who improved, but not worsened with therapy. This has provided the false impression that fibrosis has improved, when in fact no net loss of fibrosis has occurred.

This point is illustrated in Figure 5.2, which represents data from a previous study that evaluated the effects of various anti-HCV treatments on fibrosis. Among those patients who achieved SVR, 25% had less fibrosis, 7% more fibrosis, and 68% no change in the degree of fibrosis when pre- and posttreatment liver biopsy specimens were compared. However, since there is no logical reason why 7% of patients with SVR should have fibrosis progression, this most likely represents sampling variation. That is, either the pretreatment biopsy underestimated or the posttreatment biopsy overestimated the degree of fibrosis present. Thus, although the authors of this analysis suggested that 25% of patients with SVR have fibrosis regression, the actual percentage of patients with improvement in fibrosis was only 18% (25%–7%). When this same analysis is applied to patients with relapse or nonresponse, no net improvement in fibrosis was observed following treatment. For relapse patients, 16% improved and 17% worsened, a net increase in fibrosis of 1%. For nonresponders, 17% of patients had less fibrosis and 21% had worsening of fibrosis, a net increase in fibrosis of 5%. Thus, simply stating that 16% to 17% of patients without SVR had an improvement in fibrosis is misleading. This analysis is supported by the results of another large study that also evaluated the impact of treatment on fibrosis. When both improvement and worsening of fibrosis were taken into account, no net improvement in fibrosis could be demonstrated in patients with relapse or nonresponse to interferon therapy.

It is entirely possible that some nonresponders, particularly those who have a significant reduction in serum HCV RNA level, may exhibit fibrosis regression. Unfortunately, no study has specifically evaluated this cohort independently in any organized fashion.

**HCV Treatment and HCC**

Interferon has antiproliferative effects in many cell lines and has been utilized to treat several different malignancies. Previous studies have suggested that...
Various Patterns of Virologic Response to Treatment with Peginterferon/Ribavirin.

Changes in (A) Serum HCV RNA Level and (B) Liver Inflammation Scores in Response to Treatment with Interferon alfa-2b. In this trial of maintenance therapy, patients were initially treated with interferon alfa-2b for 6 months and then underwent repeat liver biopsy. Only those nonresponders who had an improvement in liver inflammation at 6 months were enrolled in the maintenance trial and randomized to continue or stop interferon for an additional 2 years.

Patients with partial VR have a decline in serum HCV RNA by 2 log units (100-fold) or more from the pretreatment baseline. If this response occurs within the first 12 weeks after the onset of treatment with peginterferon/ribavirin, it has been referred to as an early virologic response (EVR). Virtually all patients with genotype 2 or 3 infection and up to 85% of treatment-naive patients infected with HCV genotype 1 achieve EVR. Only those patients with EVR have the ability to reach undetectable HCV RNA levels with ongoing therapy and achieve both a VR and SVR. Partial VR is an important and previously underappreciated category of response to treatment. Previous studies have suggested that a decline in HCV RNA by more than 1 to 2 log units can be associated with an improvement in hepatic inflammation, and this group therefore represents an ideal population to consider for maintenance interferon therapy.

The final pattern of response that is important to recognize is relapse. This occurs in those patients whose serum HCV RNA became undetectable during therapy but reappeared after therapy was discontinued. This occurs in approximately 20% of patients who achieve VR regardless of genotype. The risk of relapse appears to be increased in those patients who required a reduction in the dose of peginterferon and/or ribavirin during treatment. Patients with relapse represent the ultimate in partial VR and may therefore achieve the most benefit from maintenance therapy.

Standard Interferon Maintenance Therapy

The only published study of maintenance interferon therapy to date evaluated the effect of continuing standard interferon alfa-2b administered at a dose of 3 MU TIW in patients with prior nonresponse but documented histologic response. Histologic response was documented by performing a repeat liver biopsy in those patients who had detectable HCV RNA in serum following an initial 6-month course of interferon. Patients with histologic response were
then randomly assigned to remain on interferon maintenance therapy for the next 2 years or to stop treatment and be followed as a control group. Patients who remained on interferon maintenance therapy had continued suppression of serum HCV RNA and hepatic inflammation. In contrast, patients who stopped treatment had a rise in serum HCV RNA level and hepatic inflammation scores back to the pretreatment baseline (Fig. 5.4, see page 35). After 2.5 years, fibrosis improved slightly in those patients who remained on maintenance therapy and worsened slightly in those patients who were randomized to stop treatment. These changes in fibrosis were not significant in either group. These observations led other groups to initiate larger and longer trials to investigate the potential benefits of peginterferon maintenance therapy.

Peginterferon Maintenance Therapy

There are several ongoing studies of peginterferon maintenance therapy. The HALT-C trial is a randomized, controlled, open-label study designed to determine if 4 years of maintenance therapy with peginterferon alfa-2a can prevent fibrosis progression to cirrhosis, and reduce the risk of hepatic decompensation, the risk of HCC, the need for liver transplantation, and liver-related mortality. Patients enrolled in the maintenance therapy phase of this trial all had bridging fibrosis or cirrhosis and failed to achieve SVR following treatment with peginterferon/ribavirin in the first phase of the HALT-C trial. These patients were randomly assigned to receive either peginterferon alfa-2a at a dose of 90 µg QW or to discontinue both peginterferon and ribavirin and be followed in the control/no-treatment group. A total of 1100 patients have been enrolled in this trial and are currently being treated and/or closely monitored at 10 centers nationwide. At this time, approximately half the patients have received 2 years of maintenance therapy. The trial is scheduled to be completed in 2008. Several other large clinical trials are also evaluating the potential benefits of peginterferon maintenance therapy. Two of these trials, COPILOT (Colchicine PegIntron Long-Term Therapy) and EPIC (Evaluation of PegIntron in Control of Hepatitis C Cirrhosis), which are studying peginterferon alfa-2b, have similar entry criteria and study design and are planned to be completed along a similar time line as HALT-C.

Side effects of treatment are one of the greatest limitations of maintenance peginterferon therapy. These include thrombocytopenia and neutropenia, which may be common and in some cases severe in patients with advanced fibrosis or cirrhosis. Flulike symptoms, depression, and fatigue may also persist in some patients and gradually worsen in other patients with ongoing therapy. These side effects led to discontinuation of maintenance therapy in a small but definite proportion of patients enrolled in a previous trial of maintenance interferon.11,22

Another limitation of current peginterferon maintenance therapy trials is the dose of peginterferon being utilized: 90 µg QW for peginterferon alfa-2a in the HALT-C trial and 0.5 µg/kg QW in the studies of peginterferon alfa-2b. These doses have been determined rather arbitrarily, with emphasis on safety. It is entirely conceivable that these doses will be insufficient to suppress HCV RNA and hepatic inflammation and therefore not prevent fibrosis progression. Indeed, the proper dose of peginterferon and the demographic, biochemical, virologic, and histologic conditions associated with successful maintenance therapy are purely speculative at this time and will not become apparent for several more years when these trials are completed and the results become widely available.

General Recommendations Regarding Maintenance Therapy

Until the results of HALT-C, COPILOT, and EPIC are known, it remains undefined whether maintenance therapy with peginterferon will be beneficial for patients with chronic HCV infection who have failed to achieve SVR. However, based upon the results of previous trials, some common sense recommendations can be made at this time (See Table 5.2).
The use of peginterferon maintenance therapy should be considered only in patients with advanced fibrosis or cirrhosis and preserved hepatic function. At this time, it is unrealistic to expect that this approach could reduce the need for liver transplantation in patients with decompensated cirrhosis and/or a prior complication of cirrhosis (ascites, variceal hemorrhage, or hepatic encephalopathy). Indeed, previous studies have suggested that interferon therapy may actually increase mortality in this group of patients. Maintenance therapy should not be considered in patients with mild or portal fibrosis. Although some patients with mild or no fibrosis may experience disease progression, it will take decades for such patients to develop significant fibrosis or cirrhosis. As a result, the potential side effects and cost of therapy cannot be justified. Rather, such patients should be followed prospectively and consideration should be given to repeating the liver biopsy at a minimum of 5-year intervals to monitor for fibrosis progression. Whether the use of serum fibrosis marker tests could be an accurate substitute for repeat biopsy in this setting has never been explored.

The only exception to this might be in those patients with significant extrahepatic manifestations of chronic HCV infection, such as symptomatic cryoglobulinemia, glomerulonephritis, and B-cell lymphoma, and where the initial course of peginterferon provided clear symptomatic and/or objective benefit for these patients.

The pattern of the previous VR is likely to be one of the most important factors in identifying patients who derive benefit from peginterferon maintenance therapy. Patients with prior relapse and with significant fibrosis (F3–4) are probably the best candidates for this approach since HCV RNA can potentially remain undetectable with maintenance therapy. Patients with a partial VR may also be an acceptable group for ongoing treatment since a marked decline in serum HCV RNA level has been associated with a decline in hepatic inflammation. In contrast, patients with a null response and no significant decline in the serum level of HCV RNA are unlikely to benefit from peginterferon and should not be considered candidates for maintenance therapy at this time.

The final issue to consider is the dose of peginterferon to be utilized for maintenance therapy. None of the previous or current studies have evaluated the impact of various doses of peginterferon on serum HCV RNA level and liver histology in the absence of SVR, and it is conceivable that a higher dose of peginterferon may suppress HCV RNA more effectively. It is therefore rational to initiate peginterferon as maintenance therapy at “full dose” for 12 weeks and then gradually reduce this at 3-month intervals to the lowest dose that suppresses HCV RNA to the greatest degree. However, when utilizing this approach it is imperative that common sense be employed and the need to balance side effects with HCV RNA suppression be carefully considered.

REFERENCES

Key Points

• The needs of many patients with hepatitis C are not met by currently available therapies.

• New therapies in development target different mechanisms of action, and therefore are likely to be additive or theoretically replace existing therapies; however, combination regimens will be necessary to improve response rates and limit the development of resistance.

• Strategies for the development of new agents include enhancements to available drugs to improve safety/efficacy, inhibition of hepatitis C virus (HCV) enzymes necessary for viral replication, and antifibrotic approaches to potentially improve outcomes in patients who are unable to successfully eradicate the virus.

• Many new compounds are in early and later stages of clinical trials, the results of which are eagerly awaited.

Enhancing Current Therapies: Modified Forms of Interferon and Ribavirin-Like Molecules

Interferons have been the mainstay of therapy for chronic HCV infection. Human interferons are classified according to which cell surface receptor they bind. Type 1 interferons bind to the interferon alpha heterodimeric receptor, including alfa, beta, omega, and tau subtypes. Type 1 interferons include the most commonly used pegylated interferon products, peginterferon alfa-2a and peginterferon alfa-2b. Interferon gamma is a type 2 interferon that binds to a different receptor. Consensus interferon is a second-generation cytokine specifically engineered to contain the most common amino acids from the nonallelic type 1 interferon alfa subtypes. It is at least as effective as endogenous type 1 interferons.

Albumin-interferon alpha (Albuferon®), a fusion protein of interferon alfa and human serum albumin that has markedly improved pharmacokinetics, is entering large clinical trials. A phase II study is in progress and was recently reported at AASLD. In this study, albumin-interferon alfa produced biphasic viral decline with a strong early response in prior interferon nonresponders and a favorable safety profile. Larger phase II trials of albumin-interferon alfa in combination with ribavirin are due to start soon in nonresponders and treatment-naive patients. Other second-generation interferons, such as omega interferon, are also entering clinical trials. Their efficacy in various populations, safety, and clinical utility will need to be further explored.

Currently available interferons are delivered via subcutaneous injections, and alternative sustained-delivery methods are being explored and evaluated. Many attempts have been made to develop an orally available drug that can induce or deliver interferon, but it has been difficult to develop a product that delivers effective doses to the liver. Few candidate compounds have made it to clinical trials for viral hepatitis. Those farthest along the pipeline include the imidazoquinolones (imiquimod [Aldara®] and resiquimod®), nucleoside analogs (ANA245), and a CpG oligonucleotide (Coley Pharmaceuticals). Imiquimod, which is approved as a topical dermatologic agent, has been associated with toxicity, probably from cytokine induction, in humans. Early reports from phase II trials of resiquimod suggest a lack of specific antiviral activity. We are far from
Table 6.1.
The HCV Pipeline.*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified Forms of Interferon</strong></td>
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<tr>
<td>Actimmune&lt;sup&gt;®&lt;/sup&gt; (interferon gamma 1-b)</td>
<td>IFN gamma 1-b</td>
<td>InterMune Inc</td>
<td>Phase II</td>
</tr>
<tr>
<td>Albuferon&lt;sup&gt;TM&lt;/sup&gt; (albumin-interferon alpha)</td>
<td>Fusion protein of IFN alpha-human serum albumin</td>
<td>Human Genome Sciences</td>
<td>Phase II</td>
</tr>
<tr>
<td>CpG 10101</td>
<td>CpG oligonucleotide</td>
<td>Coley Pharmaceuticals</td>
<td>Phase I–II</td>
</tr>
<tr>
<td>Isatoribine (ANA245)</td>
<td>Oral IFN-like molecule</td>
<td>Anadys Pharmaceuticals, Inc</td>
<td>Phase I–II</td>
</tr>
<tr>
<td>Omega interferon</td>
<td>IFN omega</td>
<td>BioMedicines Inc, Intarcia Therapeutics Inc</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Ribavirin-Like Molecules</strong></td>
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<tr>
<td>Levovirin&lt;sup&gt;TM&lt;/sup&gt; (L-isomer of ribavirin)</td>
<td>L-isomer of ribavirin</td>
<td>Valeant Pharmaceuticals</td>
<td>Phase I (halted)</td>
</tr>
<tr>
<td>Merimepodib (VX-497)</td>
<td>IMPDH inhibitor</td>
<td>Vertex Pharmaceuticals Incorporated</td>
<td>Phase II</td>
</tr>
<tr>
<td>Viramidine&lt;sup&gt;TM&lt;/sup&gt; (1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamidine)</td>
<td>Ribavirin prodrug</td>
<td>Valeant Pharmaceuticals</td>
<td>Phase II–III</td>
</tr>
<tr>
<td><strong>Immune Modulators</strong></td>
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<tr>
<td>Ceplene&lt;sup&gt;TM&lt;/sup&gt; (histamine dihydrochloride)</td>
<td>Histamine immune modulator</td>
<td>Maxim Pharmaceuticals</td>
<td>Phase II</td>
</tr>
<tr>
<td>Zadaxin&lt;sup&gt;®&lt;/sup&gt; (thymosin alpha-1)</td>
<td>Thymosin alpha-1 immune modulator</td>
<td>SciClone Pharmaceuticals</td>
<td>Phase III</td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
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<tr>
<td>BILN 2061</td>
<td>Protease inhibitor</td>
<td>Boehringer-Ingelheim Pharmaceuticals, Inc</td>
<td>Phase II (further development halted due to animal toxicology)</td>
</tr>
<tr>
<td><strong>Polymerase Inhibitors</strong></td>
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<tr>
<td>HCV-086</td>
<td>RdRp inhibitor</td>
<td>ViroPharma/Wyeth Pharmaceuticals</td>
<td>Phase I–Ib</td>
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<tr>
<td>JTK-003</td>
<td>Nonnucleoside RdRp inhibitor (polymerase inhibitor)</td>
<td>Akro Pharma Inc</td>
<td>Phase I</td>
</tr>
<tr>
<td>NM 283 (prodrug of active molecule NM 107)</td>
<td>Nucleoside acting as RdRp inhibitor (nucleoside antiviral)</td>
<td>Idenix Pharmaceuticals Inc</td>
<td>Phase I–II</td>
</tr>
<tr>
<td>R803</td>
<td>Polymerase inhibitor</td>
<td>Rigel Pharmaceuticals</td>
<td>Phase I–II (halted)</td>
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<tr>
<td><strong>Novel Anti-HCV Therapies</strong></td>
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<tr>
<td>Civacir&lt;sup&gt;TM&lt;/sup&gt; (hepatitis C immune globulin, [human])</td>
<td>Pooled HCig (polyclonal antibody)</td>
<td>Nabi Biopharmaceuticals</td>
<td>Phase I–II</td>
</tr>
<tr>
<td>HepeXTM-C (formerly XTL002)</td>
<td>Anti-HCV antibody (monoclonal antibody)</td>
<td>XTL Biopharmaceuticals</td>
<td>Phase II</td>
</tr>
<tr>
<td>IDN-6556 (IV and oral)</td>
<td>Pancaspase inhibitor</td>
<td>Idun Pharmaceuticals, Inc</td>
<td>Phase II</td>
</tr>
<tr>
<td>ISIS-14803</td>
<td>Anti-IRES antisense oligonucleotide</td>
<td>Isis Pharmaceuticals, Inc/Elan</td>
<td>Phase II</td>
</tr>
<tr>
<td>UT-231-B</td>
<td>Iminosugar p7 inhibitor</td>
<td>United Therapeutics</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>HCV Vaccines</strong></td>
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<tr>
<td>HCV vaccine</td>
<td>Vaccine with 5 T-cell epitope peptides</td>
<td>Intercell Biomedical</td>
<td>Phase II</td>
</tr>
<tr>
<td>HCV vaccine/MF59</td>
<td>Structural HCV protein vaccine</td>
<td>Chiron Corporation/CSL/St. Louis University</td>
<td>Phase I</td>
</tr>
<tr>
<td>INNO 101 hepatitis C vaccine/E-1</td>
<td>Recombinant E1 protein vaccine (therapeutic vaccine)</td>
<td>Innogenetics</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

*Compounds in clinical development to treat HCV infection at the date of writing (November 2004).
determining whether any of these new agents offer improvement in efficacy or safety, and we do not yet know how they would be utilized and combined with our current antiviral therapies.

Ribavirin, a synthetic nucleoside resembling guanosine, has limited antiviral potential as monotherapy but significantly enhances the rate of sustained viral clearance when combined with interferon. Hypothesized mechanisms include alteration of the host Th1/Th2 balance, inhibition of the enzyme inosine monophosphate dehydrogenase (IMPDH), weak inhibition of the HCV polymerase, and induction of RNA mutagenesis. Alternative ribavirin molecules with improved safety profiles (ie, less hemolytic anemia) are currently being developed.

Levovirin™, the L-sugar isomer of ribavirin, has similar Th1/Th2 immunomodulatory activity, but does not inhibit IMPDH or accumulate in erythrocytes. While this drug is theoretically attractive, its development has been delayed due to issues related to absorption and insufficient delivery to hepatocytes.

Viramidine™ (1-β-D-ribofuranosyl-1H-1, 2,4-triazole-3-carboxamidine) is a prodrug of ribavirin that is targeted to the liver, where it is then converted to ribavirin and its metabolites by adenosine deaminase. It is thus preferentially retained in the liver rather than red blood cells. In phase I studies, Viramidine had a safety profile similar to ribavirin’s but was associated with less anemia in human and animal studies. Preliminary results from an ongoing phase II study of Viramidine in combination with peginterferon indicate that antiviral efficacy at week 24 of treatment appears similar to that of peginterferon/ribavirin with significantly less anemia. Final results, as well as completion of two large phase III studies, each with 900 patients, are eagerly awaited.

Other drugs with mechanisms similar to ribavirin’s are also being developed, including IMPDH inhibitors, such as merimepobid (VX-497). A small European study of triple therapy using merimepobid in combination with peginterferon and ribavirin in patients previously nonresponsive to interferon/ribavirin showed that it enhanced on-treatment response rates. Additional larger studies in nonresponders are now under way.

**Novel Agents that Target HCV Replication Enzymes**

It may be possible to inhibit viral replication by inhibiting HCV-specific enzymes (ie, NS5B polymerase, NS3 proteases, or NS3 helicase). To date, helicase inhibitors have not been evaluated in human clinical trials, but some have shown in vitro activity. Polymerase and protease inhibitors are currently being investigated both alone and in combination regimens in early-phase human clinical trials.

Protease or polymerase inhibitors alone are unlikely to replace interferon and/or ribavirin. Analogous to the situation in HIV infection and therapy, single-drug therapy that inhibits these HCV-specific viral enzymes will most likely be associated with the development of resistance. Since our current therapy for HCV infection is capable of eradicating the virus permanently, a viral-suppressive therapy with resistant variants would be an inferior option for most infected individuals. Thus, it is likely that protease and polymerase inhibitors will best be used as part of multiregimen regimens, just as in HIV. It is unclear whether the addition of these agents to current treatment regimens will allow for the use of lower doses of peginterferon and/or ribavirin, but this possibility will need to be evaluated during the clinical drug development process.

**Protease Inhibitors**

Some of the most promising results in clinical trials of new therapies come from studies of compounds that inhibit the HCV serine protease, a key enzyme in viral replication. BILN 2061 is a small, selective, noncovalent, nonpeptide potent inhibitor of NS3 serine protease. In early clinical studies, 2 days of BILN 2061 resulted in rapid, dose-dependent HCV RNA reductions of up to 3 logs with the highest doses in patients infected with HCV genotype 1 (See Fig. 6.1). This proof-of-concept study clearly showed that prompt and effective inhibition of HCV protease efficiently blocked viral replication. Less impressive reductions in viral levels were seen in non-1 genotype infected patients. HCV RNA levels progressively returned to baseline within 1 week after treatment discontinuation. Despite these earlier successes, development of this compound has been placed on hold because of animal toxicology findings.

**Figure 6.1.**

**Virologic Efficacy of 500 mg BILN 2061 Twice Daily (Amplicor Assay) in Patients with Minimal Liver Fibrosis.** Dotted lines represent control patients, solid lines represent treated patients, circles represent drug-naive patients (na), squares represent patients who did not respond to anti-HCV therapy (NR), upper and lower intermittent lines represent the upper and lower limits of detection of the Amplicor assay, and black triangles represent administration of BILN 2061.

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Polymerase Inhibitors

Polymerase inhibitors may be nucleoside analogues, nonnucleoside inhibitors, or pyrophosphate analogues. Nonnucleoside inhibitors and pyrophosphate analogues are currently used in managing other types of viral infections (ie, HIV and herpes, respectively), and certain candidate compounds have been identified that may be active in HCV infection.

NM283 is an orally bioavailable prodrug of NM107, a ribonucleoside analogue. Early data from a dose-escalation study indicate that NM283 reduces viral load by 0.7 to 1.0 logs after just 2 weeks in HCV-infected chimpanzees and humans (See Fig. 6.2). Participants were all infected with genotype 1 and most were prior nonresponders. NM283 was well tolerated aside from minor gastrointestinal side effects at higher doses. Additional studies in treatment-naive patients and nonresponders are now necessary and planned.

Other Novel Approaches to Anti-HCV Therapies

Some other novel approaches to development of new therapies for hepatitis C that are in preclinical and clinical development include ribozymes, antisense oligonucleotides, and RNA interference. Other strategies being explored include infusions of hyperimmune anti-HCV immunoglobulins, therapeutic vaccines, and ligands that block cell-surface receptors preventing entry of HCV into the cells.

Ribozymes are catalytic RNA molecules that cleave specific sequences of RNA. Heptazyme is a synthetic, stabilized 33-mer HCV-specific ribozyme that selectively cleaves HCV RNA in the internal ribosome entry site, thereby inhibiting viral replication. In a phase II study, Heptazyme monotherapy, when dosed at 100 mg/m² BID for up to 8 weeks, reduced HCV RNA levels in about 9% (3/33) of treated patients. However, clinical investigations have been halted due to toxicology observations that emerged in animal models.

Viral genomes contain many unique nucleic acid sequences not present in the human genome, which can serve as virus-specific antisense targets. Several research groups have identified antisense oligonucleotides that inhibit HCV RNA translation in cell-free systems and cell cultures. One such compound, ISIS-14803, a 20-mer deoxynucleotide, is complementary to the highly conserved internal ribozyme entry site surrounding the translation codon and is widely distributed in the liver. In two clinical studies, ISIS-14803 monotherapy reduced HCV RNA plasma levels in a dose-related manner: viral reductions of 1.3 to 2.2 logs were seen in 3/10 patients given 2 mg/kg, and reductions of 1.0 to 3.8 logs were seen in 6/20 patients given 6 mg/kg doses twice weekly. Treatment was associated with transient flares in alanine aminotransferase (ALT) levels to 1 to 30 times the upper limit of normal, the mechanisms of which remain unclear. (See Fig. 6.3).

RNA interference (RNAi) is a newly discovered natural process in which cells downregulate gene expression by destroying a specifically targeted mRNA. A double-stranded RNA serves as a molecular guide to downregulate expression posttranslationally, mediating the RNAi process inside the cell. Compounds now in preclinical investigations include small interfering RNA (siRNA), which are biologically active short fragments of 20 to 23 residues, and expressed interfering RNA (eRNA).

It has also been determined that long-alkyl-chain iminosugar derivatives inhibit HCV p7 ion channels. These agents, which have low toxicity profiles in animals, were previously shown to have antiviral activity against bovine viral diarrhea virus. A phase II clinical trial of one of these compounds, UT-231-B (United Therapeutics Inc), is now under way in hepatitis C.
A pancaspase inhibitor that inhibits apoptosis has been administered for 14 days to hepatitis C patients who have not responded to prior antiviral therapy. The preliminary results indicate that the drug reduces liver enzyme levels, but has no antiviral effect. Additional studies are in progress.

Antifibrotic therapies would be an attractive option for nonresponders in order to slow the progression of liver disease when viral eradication is no longer an attainable goal. Low-dose maintenance interferon is discussed elsewhere in this publication (please refer to “Lack of Sustained Response in Hepatitis C: Considering Maintenance Therapy”). Currently, no drugs have been proven to specifically reduce/prevent fibrosis in the human liver; however, several antifibrotic strategies are theoretically possible (See Table 6.2).

Conclusions

Peginterferon/ribavirin is expected to remain the standard of care for treatment of hepatitis C for at least the next 5 years as investigations into novel types of therapies advance. Various therapies with different mechanisms of action are under investigation for the treatment of chronic hepatitis C in hopes that they will eventually offer improvements in efficacy and tolerability. They each have different advantages and disadvantages. Continued investigations should reveal more about their efficacy and safety profiles, as well as their potential roles in combination with existing treatments. Clinical trials must also address how these drugs should be used and in what patient populations. Antifibrotic therapies are most likely to be reserved for patients who fail to respond to potentially curative antiviral regimens. Direct viral enzyme inhibitors might be particularly useful in preventing recurrent hepatitis C posttransplantation. How these newer agents may be used in combination with our current standard of care and identification of appropriate patient populations will require carefully controlled clinical trials. The aims should be to improve efficacy and tolerability, while at the same time limiting or preventing the development of resistance.

Table 6.2.

<table>
<thead>
<tr>
<th>Antifibrotic Approaches</th>
<th>Investigational Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent activation of stellate cells by reducing inflammation or host response</td>
<td>Ursodeoxycholic acid; TNF alfa antagonists</td>
</tr>
<tr>
<td>Downregulate stellate cell activation by reducing oxidative stress</td>
<td>Antioxidants (eg, vitamin E); interferon; hepatocyte growth factor; peroxisome proliferator activated nuclear receptors (eg, thiazolidinediones)</td>
</tr>
<tr>
<td>Neutralize stellate cell responses; inhibit matrix production and accelerate matrix degradation</td>
<td>Inhibitors of proliferative cytokines (eg, PDGF, FGF, TGF alfa and beta, endothelin-1); halofuginone</td>
</tr>
<tr>
<td>Stimulate stellate cell apoptosis</td>
<td>Gliotoxin</td>
</tr>
<tr>
<td>Increase scar matrix degradation by stimulating cells that produce matrix proteases, inhibiting their downregulation, or by direct administration of matrix proteases; enhance matrix resorption</td>
<td></td>
</tr>
</tbody>
</table>

A pancaspase inhibitor that inhibits apoptosis has been administered for 14 days to hepatitis C patients who have not responded to prior antiviral therapy. The preliminary results indicate that the drug reduces liver enzyme levels, but has no antiviral effect. Additional studies are in progress.

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References

Key Points

- Liver transplantation is the treatment of choice in selected patients with complications of end-stage liver disease (ESLD), and is performed in more than 5000 patients annually in the United States.
- Hepatitis C virus (HCV) is the leading indication for liver transplantation; yet recurrence of infection, which is universal, may result in progressive disease of the allograft leading to premature graft failure.
- Discrepancies between numbers of patients with ESLD in need of transplantation and available donors have led to strategies to increase the donor pool, including living-related donation and expanded criteria for donors.
- Indications for liver transplantation continue to increase such that patients who had previously been excluded are now considered appropriate candidates. These include those with active hepatitis B virus (HBV) infection, and select patients with hepatocellular carcinoma (HCC) or HIV infection.
- Management of pretransplantation complications of disease, such as viral infections (hepatitis B and C) and complications of portal hypertension (eg, bleeding esophageal varices and ascites), may reduce pretransplantation complications and improve the medical conditions of those undergoing liver transplantation.
- The Model for End-Stage Liver Disease (MELD) score, which is based on “objective” prognostic markers, was introduced in order to improve the fair allocation of organs to individuals at highest risk of death without transplantation.
- Improved management of posttransplantation complications such as prevention of rejection and opportunistic infections, as well as technical improvements in the surgical procedure itself, have resulted in excellent posttransplantation outcomes.

Introduction

Over the past 3 decades, liver transplantation has progressed from an experimental intervention to the standard of care for appropriate patients with acute, fulminant liver failure and for patients with ESLD. One-year patient and graft survivals are excellent at 80% to 90% in most centers, and 3-year survivals are good, in the range of 70%. HCV remains the leading indication for liver transplantation in the United States and Europe, accounting for approximately 40% of all transplantations. While short-term outcomes are acceptable, there is significant concern about long-term patient and graft survival—concern resulting largely from progressive HCV disease of the allograft.

The number of patients with complications of ESLD is rising such that there are now more than 5000 patients undergoing liver transplantation every year in the United States, and almost 20,000 patients awaiting transplantation. These statistics do not take into account populations with complications of liver disease who are not, for a variety of reasons, appropriate candidates for liver transplantation. Thus, more than 20,000 individuals in the United States alone are in need of advanced liver disease care.

Management of complications of liver disease has improved greatly in recent years. We now know that reduction in portal pressure through nonselective beta blockers may prevent life-threatening variceal bleeding. Management of variceal bleeding has also improved with band ligation of esophageal varices. Improvement has also been made in primary prevention of bleeding in those with moderate-to-large esophageal varices, and in secondary treatment of varices after the initial bleed. Management of ascites has improved with prevention of spontaneous bacterial peritonitis through the administration of oral antibiotics, and control of diuretic-resistant ascites through large-volume paracentesis and/or placement of transjugular intrahepatic portosystemic shunts. For some disease states, such as hepatitis B, hepatic decompensation can be improved through suppression of viral replication, with a decrease in the development of clinical complications and avoidance of liver transplantation in individual patients. However, for most diseases, once hepatic decompensation occurs, clinical progression is inevitable and life expectancy is markedly reduced unless liver transplantation becomes available. For these individuals, liver transplantation offers a very real opportunity for improved survival and improved quality of life.

Indications for Liver Transplantation and Selection of Appropriate Candidates for Transplantation

All patients with advanced liver disease are potential candidates for liver transplantation if they have access
to care, have a life expectancy shortened in the near term by their disease, and lack contraindications for transplantation (Table 7.1). Historically, certain diseases such as HBV infection with active viral replication were considered to be absolute contraindications for transplantation because HBV infection of the graft frequently resulted in graft failure and death. However, effective therapeutic interventions have changed the outcome such that 1-year posttransplantation survival is about 80% to 90%, and HBV disease is now considered to be an excellent indication for transplantation. HIV infection has also historically been considered an absolute contraindication to liver transplantation, but this too has been re-examined. Early data suggest that outcomes with liver transplantation in selected patients with HIV infection may be comparable to those who are HIV negative. Thus, HIV-infected individuals are increasingly being considered and accepted as candidates for liver transplantation.

Historically, other disease states have been routinely considered for liver transplantation; however, there is increasing concern that posttransplantation outcomes are poor and liver transplantation should not be undertaken in these populations. These include:

- Patients with HCC that has extended outside the liver, involving the portal vein, as well as those with >3 lesions or a single lesion >5 cm (Table 7.1)
- Those with cholangiocarcinoma other than highly selected patients who have negative margins without lymph-node involvement at surgical resection
- Those who have previously undergone liver transplantation and are in need of retransplantation because of graft failure from recurrence of the viral hepatitis C

This third group is most pertinent to patients with HCV infection prior to liver transplantation. HCV infection of the graft is universal in those with pretransplantation infection, and disease progression in the graft is 10-fold greater than that prior to liver transplantation. Progressive liver disease resulting in cirrhosis and graft failure has led to consideration of retransplantation in these patients, although outcomes are worse than with the initial transplantation.

Indications, as well as relative and absolute contraindications to transplantation, are listed in Table 7.1. There are center-to-center variations in some of these criteria, including duration of demonstrated abstinence from alcohol and/or illicit drugs, cigarette smoking, HIV status, definitions of adequate compliance and/or social support, use of methadone, size of a single lesion in a patient with HCC, and whether the size of the lesion can be measured after downstaging through radiofrequency ablation and/or hepatic arterial embolization. Definitions of extrahepatic co-morbid conditions also vary from

| Table 7.1. Indications and Contraindications for Liver Transplantation. |

### Indications

- Complications from the following liver diseases
  - HBV
  - HCV
  - Alpha-1 antitrypsin deficiency
  - Alcoholic cirrhosis
  - Hemochromatosis/Wilson’s disease
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - HCC (confined to the liver and with <3 lesions, none ≥3 cm in diameter or a single lesion >5 cm in diameter)
  - Cryptogenic cirrhosis, some of which may be secondary to nonalcoholic fatty liver disease (NAFLD)
  - Autoimmune hepatitis
  - Acute liver failure of various etiologies, including viral hepatitis and drug-induced liver disease
  - Pediatric diseases, including biliary atresia
  - Liver disease (largely HCV or HBV) in HIV-infected individuals, in whom the HIV is well controlled
  - Retransplantation for early postoperative complications, such as primary nonfunction (PNF) of the graft and hepatic arterial thrombosis

### Relative contraindications

- Life-determining extrahepatic disease, except renal failure
- History of coronary artery disease
- Uncontrolled bacterial infections
- Uncontrolled HIV infection
- Cholangiocarcinoma localized to the liver
- HCC with 1 lesion 5–7 cm in diameter
- Methadone use
- Cigarette smoking
- Retransplantation for late postoperative complications, such as progressive HCV disease

### Absolute contraindications

- Noncompliance with medications and/or clinic visits
- Cancer outside liver with an estimated life expectancy of <5 years
- Lack of social support
- Active substance use (alcohol, marijuana, and other illicit drugs)
- HCC with >3 lesions or a single lesion >7 cm in diameter
- Cholangiocarcinoma without clear surgical margins
center to center. For example, some centers consider hepatopulmonary syndrome to be an indication for transplantation, whereas others exclude such patients because of high risk of perioperative complications. Some centers consider patients with hemochromatosis good candidates for liver transplantation, yet others frequently exclude these patients because of increased risk of perioperative complications from cardiomyopathies and arrhythmias associated with cardiac iron deposition. The referring physician should work closely with his or her local transplant center to understand some of the differences that occur locally and, when necessary, refer the patient to another center whose criteria may be more suitable for that patient.

Organ Allocation and Donor Criteria
Allocation of organs for those considered appropriate candidates for liver transplantation has changed significantly in recent years (See Table 7.2). In the past, patients received an organ based on severity of liver disease measured by intensive care unit status and the Childs-Pugh-Turcotte score (which includes serum bilirubin, albumin, prothrombin time, and presence of ascites or encephalopathy); time they had been on the waiting list for transplantation; and local availability of organs in the hospital’s organ-procurement organization. As the number of patients awaiting liver transplantation grew, discrepancies between centers in terms of access to transplantation worsened. This occurred in part because many of the criteria used to allocate organs were subjective, and there were differences in the ways centers defined these criteria. In order to rectify some of these problems, a new method for organ allocation that eliminated waiting time and reduced the number of subjective criteria was implemented in 2002. The MELD model was introduced in an attempt to allocate organs to those at highest risk of dying without transplantation. The formula is based on serum creatinine, bilirubin, and International Normalized Ratio for prothrombin time, with additional points being given to patients with HCC. To date, while still under evaluation, the MELD score does appear to be more accurate than prior methods in predicting pretransplantation mortality, and as such MELD is an advance towards the goal of achieving distribution of organs to those in greatest need. In general, patients with the highest MELD scores derive the greatest benefit with transplantation. In contrast, patients with MELD scores of <15 likely do not derive a 1-year survival benefit with transplantation compared with the natural history of the underlying liver disease. Evaluated prospectively, MELD appears to improve rate of transplantation and pre- as well as early posttransplantation mortality. The MELD system remains under evaluation, however, since significant center-to-center differences in the severity of liver disease in those undergoing liver transplantation still exist. In many centers, patients are unlikely to undergo transplantation with MELD scores <25 to 30, whereas in other centers, patients with MELD scores of <15 are still receiving organs. The MELD scoring system has further limitations in that MELD is not as accurate at predicting posttransplantation survival as it is at predicting pretransplantation survival. In addition, MELD may be associated with reduced posttransplantation survival in certain high-risk patients, particularly those with HCV disease and high MELD scores. Nevertheless, MELD and PELD (the score for pediatric ESLD patients) are likely to remain the allocation systems used for the foreseeable future.

Another major change in organ donation in the recent past has been the use of adult-to-child and subsequently adult-to-adult living donor liver transplants (LDLT). For adult-to-child living donation, the left lateral segment of the liver is removed and transplanted into the pediatric recipient. For adult-to-adult living donation, the larger right lobe of the liver is removed and implanted into the recipient. Particularly for adult-to-adult LDLT, careful selection of the donor based on size characteristics is necessary to minimize risk to either the donor or the recipient. Last year, 321 LDLTs were performed in the United States. One-year patient and graft survivals are similar in recipients of LDLT to those of deceased donor (DD) liver transplantation. This is also true for the “sicker” patients (those with a MELD score of >25) undergoing LDLT, in which 1-year survival is 66%. Long-term data from outcomes of both donors and recipients will be necessary to evaluate accurately the risks and benefits of LDLT.

Because of the severe donor shortage, other strategies have been used to expand the donor pool. These include use of donors that historically had been considered “too high risk” (See Table 7.2). It is

<table>
<thead>
<tr>
<th>Table 7.2. Recent Changes in Organ Allocation and Donor Characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- MELD score for distribution of adult donors</td>
</tr>
<tr>
<td>- PELD score for distribution of donors to children</td>
</tr>
<tr>
<td>- Selective use of expanded donor criteria including</td>
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<td></td>
</tr>
<tr>
<td>- Adult-to-child LDLT</td>
</tr>
<tr>
<td>- Adult-to-adult LDLT</td>
</tr>
</tbody>
</table>

MELD = Model for End-Stage Liver Disease; PELD = Pediatric End-Stage Liver Disease; LDLT = living donor liver transplant.
important to note that the risk to the recipient of primary nonfunction (PNF) of the graft is probably additive if more than one of these high-risk characteristics are present in the donor. The risk to the recipient of an organ from a high-risk donor is also dependent in part on characteristics of the recipient. Older donors and donors with hepatic steatosis appear to be particularly problematic for HCV-infected recipients, placing them at high risk of progressive posttransplantation HCV disease. Stable recipients with low MELD scores are better able to tolerate the added stress of high-risk donors than are severely ill recipients with high MELD scores in whom posttransplantation survival is impaired if the donor function is marginal. Livers from selected donors with low-level HBV infection (anti-HBcore) or HCV infection (anti-HCV positive) can likely be used safely in HBV-infected (HBsAg positive) or HCV-infected (anti-HCV and HCV RNA positive) recipients respectively, but not in those without these pretransplantation infections. By law, HIV-infected donors cannot be used for transplantation irrespective of the serostatus of the recipient. Xenotransplantation has been used in the past for critically ill recipients predicted to have high mortality in the absence of transplantation. However, outcomes with xenotransplantation have been poor, largely due to hyperacute rejection and posttransplantation infections. Nevertheless, as the number of patients on the waiting list for liver transplantation continues to increase, creative and innovative ways to expand the donor pool will need to be explored.

Posttransplantation Management and Complications

Historically, posttransplantation rejection was the major complication of all solid-organ transplantation including liver transplantation. With advances in immunosuppressive therapy, graft loss from acute and/or chronic rejection is much less frequent than in the past. There are three main classes of drugs used to prevent acute rejection: corticosteroids, calcineurin inhibitors, and antiproliferative agents (See Table 7.3). Unfortunately, these effective drugs come with side effects that contribute to posttransplantation complications, such as diabetes, hypertension, renal insufficiency, and increased susceptibility to infection (See Table 7.4).

Generally, two or three agents are used to prevent rejection in the immediate posttransplantation period. Corticosteroids have been used for decades to prevent as well as treat rejection, thus improving graft survival. Unfortunately, steroids, particularly at high doses, are associated with significant side effects, notably diabetes, hypertension, osteoporosis, psychosis, and infection. While steroids are still frequently used in the immediate posttransplantation period, attempts are made to reduce and, when possible, discontinue steroids within 6 to 12 months of transplantation. Calcineurin inhibitors, such as cyclosporine and tacrolimus, form the backbone of long-term immunosuppressive regimens, yet these drugs also have substantial toxicities, notably
hypertension, renal insufficiency, and neurotoxicities including seizures. Despite these toxicities, the majority of liver-transplant recipients remain on cyclosporine or tacrolimus long term. The third class of drugs used to prevent acute cellular rejection includes the antiproliferative agents azathioprine and mycophenolate mofetil (MMF). MMF appears to be more effective than azathioprine in reducing the incidence of acute rejection, and MMF may also prevent chronic rejection. Major toxicities of MMF are bone marrow suppression (leukopenia, anemia, and thrombocytopenia) and gastrointestinal side effects.

In addition to these three classes of drugs, antilymphocyte agents, such as OKT3, and newer monoclonal antibody preparations, such as basiliximab and daclizumab (See Table 7.3), are used for the treatment of steroid-resistant rejection. Sirolimus, also called rapamycin, is the first in a new class of immunosuppressive agents and has been used in combination with calcineurin inhibitors. The major advantage of this drug is its lack of nephrotoxicity, so that it can be used preferentially in patients with renal insufficiency. Toxicities of sirolimus include leukopenia, thrombocytopenia, and hyperlipidemia.

With current surgical techniques, complications like hepatic arterial thrombosis and biliary stenoses/biliary leaks are relatively infrequent, but if they do occur, they are seen early in the postoperative period (See Table 7.4). Problems associated with the donor, such as PNF, and problems related to complications of immunosuppressive therapies, including increased susceptibility to infection, diabetes, hypertension, and renal insufficiency, are summarized in Table 7.4. Many of the drugs used for posttransplantation management are prescribed in order to prevent and/or treat these posttransplantation complications (See Table 7.3).

While short-term outcomes of LDLT appear to be comparable to those for DD, certain complications, namely postoperative biliary complications, are seen more frequently with LDLT. A complication specific to LDLT is “small-for-size syndrome,” which is characterized by prolonged cholestasis, particularly in adult recipients of grafts that are too small. There is also concern that recurrence of HCC and HCV infection may be more severe in recipients of LDLT, compared with recipients of DD, although the data are too preliminary to draw definitive conclusions.

### Recurrent Disease Posttransplantation

Recurrence in the allograft of the primary cause of liver failure leading to transplantation is increasingly being recognized as a posttransplantation complication. Diseases that have been shown to recur are summarized in Table 7.5. The most devastating consequences of recurrence to the recipient have been associated with HBV and hepatic malignancies. However, effective interventions with specific HBV therapies (lamivudine and/or adefovir) in combination with hepatitis B immune globulin have largely prevented posttransplantation HBV disease (Table 7.6, see page 50). In addition, while initial outcomes of transplantation for HCC were dismal, liver transplantation in highly selected patients with HCC has resulted in excellent survival. Outcomes with liver transplantation for cholangiocarcinoma are generally
dismal, making cholangiocarcinoma an absolute contraindication to transplantation in many centers. HCV, with or without alcoholic liver disease, is the leading indication for liver transplantation. Recurrent infection is universal in those with pretransplantation viremia. While initial outcomes are comparable to those without HCV infection, it has become apparent that over time, HCV disease can be progressive, leading to increased risk of graft loss and reduced patient survival. Moreover, progression of fibrosis is increasing in patients who have undergone liver transplantation in recent years. Variables associated with posttransplantation HCV disease progression include HCV RNA levels at the time of transplantation, potent immune suppression in the early posttransplantation period, and in some studies, genotype 1b infection. Reasons for the worse outcomes with transplantation in recent

Table 7.6.

Management of Posttransplantation Viral Hepatitis B and C.

<table>
<thead>
<tr>
<th>Pretransplantation Management</th>
<th>Goal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Low-dose” peginterferon/ribavirin in HCV-infected patients accepted for liver transplantation*</td>
<td>To eradicate virus and reduce the risk of posttransplantation graft infection</td>
<td>Treatment should only be undertaken in center with experience because of potentially life-threatening infections and cytopenias</td>
</tr>
<tr>
<td>Lamivudine plus or minus adefovir† in decompenated HBV cirrhosis, in order to suppress viral replication</td>
<td>To reduce the risk of posttransplantation graft infection and possibly improve hepatic synthetic function</td>
<td>May reduce incidence of clinical complications and abrogate need for liver transplantation</td>
</tr>
</tbody>
</table>

| Peritransplantation Management |
|-------------------------------|------|---------|
| Hepatitis C immune globulin (HClg) has been used experimentally | To neutralize circulating HCV RNA at the time of transplantation | Not proven to be effective |
| Intravenous hepatitis B immune globulin (HBIg) has been used either alone or in combination with lamivudine | To neutralize circulating HBV DNA at the time of transplantation | Considered standard-of-care |

<table>
<thead>
<tr>
<th>Posttransplantation Management</th>
<th>Goal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon/ribavirin‡ has been used pre-emptively early in the posttransplantation period</td>
<td>To prevent development of posttransplantation disease</td>
<td>Complications of therapy include profound ribavirin-associated anemia and increased risk of infection and/or allograft rejection</td>
</tr>
<tr>
<td>Peginterferon/ribavirin‡ for histologically proven HCV disease</td>
<td>To treat progressive posttransplantation HCV disease and prevent allograft failure</td>
<td>Complications of therapy are higher and likelihood of clearance lower than treatment of nonimmunosuppressed patients with HCV disease</td>
</tr>
<tr>
<td>Lamivudine plus HBIg</td>
<td>To prevent HBV infection of the allograft</td>
<td>Dose and duration of HBIg unclear; route of administration (intravenous versus intramuscular) controversial</td>
</tr>
<tr>
<td>Lamivudine with or without adefovir§</td>
<td>To treat established HBV disease of the graft</td>
<td>Combination therapy probably superior to either drug alone*</td>
</tr>
</tbody>
</table>

*Peginterferon dose reduced depending on absolute neutrophil count and/or platelet count; full dose rarely indicated.
†Lamivudine monotherapy can effectively suppress HBV replication but is associated with high likelihood of resistance over time, resistance that can result in hepatic decompensation. The addition of adefovir can prevent emergence of lamivudine resistance, providing rationale for combination therapy.
‡Ribavirin dose reduced depending on renal function and baseline hemoglobin. Full-dose ribavirin rarely tolerated. Peginterferon dose may be reduced depending on absolute neutrophil count and/or platelet count.
§Doses of both lamivudine and adefovir should be modified for renal insufficiency.
years are under investigation, but likely include increased use of marginal donors, as well as changes in immunosuppressive regimens. Strategies to prevent and treat posttransplantation HCV disease are summarized in Table 7.6. While outcomes of transplantation for HCV are not so sufficiently poor that HCV is considered a contraindication to liver transplantation, retransplantation for progressive HCV disease is rarely undertaken.

A number of other liver diseases recur following liver transplantation, but consequences of recurrent disease are typically mild and rarely lead to graft failure. These include primary biliary cirrhosis, autoimmune liver disease, and primary sclerosing cholangitis, all of which probably recur in a proportion of those who have undergone liver transplantation for these primary diseases. Patients who undergo liver transplantation for alcoholic liver disease are at risk for recidivism, and even with careful pretransplantation screening, it appears that many return to drinking following liver transplantation. Fortunately, recurrent alcoholic hepatitis and/or cirrhosis appear to be rare. The primary defect in hemochromatosis—a genetic disorder characterized by hyperabsorption of intestinal iron—would logically be predicted to persist following liver transplantation; however, clinically apparent iron overload of the allograft appears to be rare. Nonalcoholic fatty liver disease (NAFLD) is increasingly being recognized as a cause of advanced liver disease and may account for a proportion of patients who would previously have been characterized as having cryptogenic cirrhosis. NAFLD is caused at least in part by insulin resistance, a metabolic disorder that likely persists and may even worsen after liver transplantation, putting patients at risk for recurrent hepatic steatosis.

Summary

Liver transplantation has become routine in the management of life-threatening acute and chronic liver disease. This success, however, has contributed to major shortages of suitable donors. In order to address these shortages, as well as to attempt to provide organs to those at highest risk of dying in the absence of transplantation, there have been substantial changes in policies for organ allocation, as well as changes in criteria for acceptable donors. Technical problems associated with liver transplantation have been largely solved, and risk of rejection with current immunosuppressive regimens is low. Thus, the major complications of liver transplantation relate to recurrence of the primary disease and adverse effects of drugs used to prevent acute and chronic rejection. Future breakthroughs in liver transplantation will likely depend on continued expansion of the donor pool and effective therapies to prevent recurrent posttransplantation disease.

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18. Sung JJY, Lai JY, Zeuzem S, et al. A randomised double-blind phase II study of lamivudine (LAM) compared to lamivudine plus adefovir dipivoxil (ADV) for treatment naive patients with chronic hepatitis B (CHB); week 52 analysis [abstract 4313]. Presented at: 38th annual meeting of the European Association for the Study of the Liver (EASL); July 3-6, 2003; Geneva, Switzerland.
VIII.

RELATIONSHIP BETWEEN CHRONIC HCV INFECTION AND HEPATOCELLULAR CARCINOMA

Adrian M. Di Bisceglie, MD

Key Points

• Chronic viral hepatitis is the single largest risk factor for hepatocellular carcinoma (HCC) in the world.

• Although chronic hepatitis B is the most common underlying liver disease in Asia and Africa, chronic hepatitis C is more prevalent in western Europe and the United States.

• Surveillance for HCC is commonly performed, although it has not been found to alter patient outcomes. Surveillance should be directed toward patients with chronic hepatitis C and cirrhosis. A commonly used approach is serial ultrasound examination every 6 to 12 months.

• Serum alpha-fetoprotein levels are frequently elevated in patients with chronic hepatitis C without HCC and may be very misleading when used to screen for HCC.

• There is evidence from retrospective studies that antiviral therapy of hepatitis C with interferon reduces the risk of HCC. This issue is currently being tested in several long-term prospective studies. The routine use of long-term suppressive therapy of hepatitis C with interferon should wait for the completion of these studies.

Historical Perspective

Until relatively recently, hepatocellular carcinoma (HCC) was something of a rarity in the developed Western world and, as a consequence, little thought was given to its etiology and treatment. Most older texts, even from as recently as the 1960s and early 1970s, placed emphasis on chemical hepatocarcinogenesis, as exemplified in rodent animal models of HCC.1 In the experimental Solt-Farber model, rats or mice were given carcinogenic agents, such as ethylnitrosourea (referred to as “initiation”), followed by phenobarbital as a “promoting” agent to produce HCC. Although this model was very convincing, the connection with human HCC was not clear. Clearly, alcoholism is associated with HCC, and alcohol is considered a chemical carcinogen, but it does not explain all of the other cases of HCC.2 Moreover, if alcohol was a major cause, why was HCC so much more common in underdeveloped countries than in the Western world, which consumes at least as much alcohol?2

It was not until discovery of the hepatitis B virus (HBV) in 1965 that more pieces began to fall into place. Evidence soon emerged of an association between chronic liver disease, HCC, and seropositivity for hepatitis B surface antigen (originally referred to as the “Australia Antigen”). Furthermore, Beasley and colleagues4 working in Taiwan demonstrated in a prospective controlled trial involving 22,000 men that HBsAg positivity was a very strong risk factor for HCC.

Throughout the 1970s and 1980s, investigators in Japan came to recognize a steady and disturbing rise in the incidence of HCC cases not related to HBV infection.5 Most of these cases were subsequently found to be associated with infection by the hepatitis C virus (HCV), which emerged in the Japanese population in the years after World War II.

Japanese investigators were also among the first to recognize that HCV-related HCC often took 2 to 3 decades to develop.6 They observed that patients who developed posttransfusion hepatitis C went through stages of acute, mild, moderate, and then severe chronic hepatitis, leading to cirrhosis and eventually HCC. Now, nearly 10 years later, the incidence of HCC is rising in the United States and western Europe.7,8 It has been speculated that the peak in cases of HCC is occurring later in the West than in Japan because the spread of HCV occurred about 10 years later, with increased use of injection drugs in the 1960s.

Epidemiology of HCC

There are marked differences in the incidence of HCC in different parts of the world, and risk factors appear to differ as well. The highest incidence rates are in southern Africa, China, and other parts of southeast Asia, where almost all cases appear to be associated with chronic HBV infection.

The incidence of HCC in southern Europe and Japan is intermediate between that of Africa and China and the other western countries, and in these regions, HCV infection appears to play a dominant role in the etiology of HCC. Nearly three quarters of cases of HCC in Spain and Italy tested positive for anti-HCV, whereas both HCV infection and HCC are much less common in Scandinavia and Britain.9,10 In the United States, HCC has been a relatively uncommon tumor, but the incidence appears to be rising at a
time when many other major cancers are declining (See Fig. 8.1). Although the reasons for this rise are not entirely clear, there is strong evidence that it may be correlated with the emergence of HCV infection in the US population, just as happened in Japan 10 to 15 years ago.

Pathogenesis of HCC

The precise mechanisms by which HCV infection leads to HCC are not known. HCV has an RNA genome that does not integrate into that of infected human cells. Almost all cases of HCV-related HCC are associated with cirrhosis or other severe underlying liver disease, which suggests that it is the long-standing process of inflammation, injury, regeneration, and fibrosis caused by HCV infection that somehow leads to cancer. Long-term follow-up studies of patients with cirrhosis due to hepatitis C have found that HCC develops at a steady rate of between 1.5% and 9% per year. The highest rates have been noted in Japan, whereas rates of HCC among European patients with cirrhosis have ranged between 1.5% and 4% per year. In a recent study of the natural history of compensated cirrhosis in 254 patients with hepatitis C, HCC developed in 65 after a median follow-up period of 93 months (approximately 2.5% per year). HCC was the most frequent complication of liver disease to arise in this group, and was the most common cause of death.

HCV core antigen has been implicated in the pathogenesis of HCC in several ways. It inhibits apoptosis and is associated with transformation of certain cells to a tumorigenic phenotype. At least one lineage of transgenic mice expressing HCV core antigen has been shown to develop HCC. The role of other HCV proteins or factors has not been evaluated extensively in HCC.

Role of Co-factors

Various co-factors have been implicated in hepatocarcinogenesis with HCV. These include coinfection with HBV, alcohol, porphyria cutanea tarda (PCT), and diabetes and fatty liver disease. The relative risk of HCC is substantially greater among patients coinfected with HCV and HBV than among those with HCV alone, both in southern Africa and Europe. Consumption of excessive alcohol is well-known to promote the progression of hepatic fibrosis due to hepatitis C, but also appears to increase the rate of development of HCC (See Fig. 8.2). PCT is an uncommon acquired metabolic condition usually associated with chronic liver disease and is manifested by photosensitive skin eruptions and increased excretion of porphyrins in the urine. As many as 70% of PCT cases are associated with HCV infection, and these individuals appear to have a higher rate of HCC than those with HCV infection alone. Finally, there is growing evidence of an association between diabetes, fatty liver disease, and HCC. Thus, a proportion of patients with HCC in the United States have been identified as having cirrhosis but no evidence of chronic viral hepatitis. Closer examination revealed that many of these patients have nonalcoholic fatty liver disease (NAFLD), often with cirrhosis. It now seems that NAFLD may potentiate the development of HCC in patients with hepatitis C.

Thus, patients with hepatitis C should be counseled strongly against excessive alcohol consumption. In addition, they should be offered vaccination against HBV if they are not already immune.

Diagnosis and Screening for HCC

Patients with HCC may present with complaints of right-upper-quadrant pain and weight loss. Radiology is the mainstay of diagnosis for HCC. Imaging of the liver with ultrasound, computed tomography, or magnetic resonance imaging shows the typical hypervascular mass within the liver. Liver biopsy may be required to confirm the diagnosis, but is not required prior to undertaking surgical resection or even liver transplantation. Serum levels of alpha-fetoprotein (AFP) are often raised in patients with HCC, but may also be elevated with chronic liver disease in the absence of HCC. Because patients with chronic hepatitis are at increased risk of HCC, it has been suggested that
they undergo screening or surveillance in order to detect HCC at an early stage. Typically this has been done by serial measurement of serum AFP combined with imaging of the liver, often with ultrasound, commonly every 6 to 12 months. Although there is little evidence that this approach improves patient outcomes, surveillance has become widely practiced.

Physicians should consider surveillance for HCC in HCV-infected patients only if they have cirrhosis, since development of HCC is extremely rare among patients with HCV infection who do not have cirrhosis. Small HCC can be detected by regular surveillance with ultrasound examination of the liver, and detection at an early stage may offer the best options for successful treatment. It must be recognized, however, that there is no definitive evidence that surveillance for HCC improves patient outcomes.

Treatment of HCC

Surgical removal of the tumor within the liver (hepatic resection) has long been the mainstay of treatment for HCC. Application of this treatment has been limited because HCC usually arises in the presence of cirrhosis, making resection more difficult. Patients with cirrhosis do not tolerate hepatic resection well as it may result in hepatic decompensation. Nonetheless, with improved surgical techniques and greater surgical experience developed over the last 20 years coupled with better patient selection, the perioperative mortality for resection of HCC has decreased substantially, to <5%. Unfortunately, only a small fraction of patients with HCC are resection candidates because of the severity of underlying liver disease or the extent of the tumor. In addition, the recurrence rate after resection for HCC has been high, on the order of 20% to 25% per year. Most of these “recurrences” are thought to be de novo tumors, which arise because of underlying cirrhosis and/or chronic viral hepatitis. This makes liver transplantation an appealing prospective therapy because it treats the underlying liver disease as well as the cancer.

Orthotopic liver transplantation (OLT) has become a common form of treatment for patients with HCC and is associated with good outcomes if patients are carefully selected. The criteria used are those originally described by Mazzaferro and colleagues from Milan and are now referred to as the Milan criteria. For OLT, HCCs should not exceed the following dimensions: a single tumor up to 5 cm or, if multiple, no more than 3 tumors, each less than 3 cm in diameter.

In recent years, tumor ablation has rivaled resection as therapy for HCC. Tumors within the liver may be ablated by injection of destructive agents, such as absolute alcohol, hot saline, and trichloroacetic acid. Alcohol is the most frequently used and, although no randomized controlled trials have been done, patient survival following alcohol ablation of HCC is very similar to that after hepatic resection for the same tumor (See Fig. 8.3). Most recently, radiofrequency ablation has emerged as another method to ablate HCC without surgery, and its use is rapidly overtaking that of alcohol injection.

Traditional chemotherapy has proven to be of little value in the treatment of HCC. Some success has been claimed for chemoembolization, a technique in which chemotherapeutic agents are infused into the hepatic artery followed by occlusion of that artery, cutting off the blood supply to the tumor.

Prevention of HCC

Because the etiology can readily be identified for most cases of HCC, attention has focused on attempts to prevent the cancer by preventing the underlying cause. A safe and effective vaccine against HBV
has been available for nearly 20 years, and vaccine programs established in Taiwan and other countries have already had an impact on the incidence of HCC (See Fig. 8.4). HCC is therefore the first human cancer to be preventable by a vaccine. Public health efforts have led to a dramatic decrease in the number of new infections with hepatitis C occurring each year in the United States. This is expected to eventually lead to a decline in the number of HCV-related HCCs, although an interim rise is anticipated due to the large number of individuals already infected with HCV.

There is growing interest in the use of antiviral therapy as a form of chemoprevention of HCC. Thus, several large retrospective studies (most from Japan), have suggested that antiviral therapy of chronic hepatitis C with interferon alfa reduces the risk of HCC. A retrospective cohort study found that HCC developed in about 4% (89/2400) of HCV-infected patients treated with interferon compared with 12% (59/490) of untreated patients (adjusted risk ratio, 0.516; 95% CI, 0.358–0.742; P < .001). The greatest benefit in reducing HCC appears to be among those who achieve a sustained virologic response (See Table 8.1). This approach is currently being evaluated in a series of long-term studies testing whether treatment with interferon alfa reduces the risk of liver disease progression in general, and HCC in particular, among patients with chronic hepatitis C and advanced fibrosis. Recent preliminary data on the use of an oral antiviral agent active against HBV (lamivudine) suggest that prolonged treatment can reduce the risk of HBV-related HCC as well.

### Future Directions

The incidence of HCC is clearly rising in the Western world; however, it is not clear how long this rise will continue. Universal infant vaccination against HBV has been introduced in most developed Western countries. The number of new cases of hepatitis C has been declining in the United States for approximately 5 years because of various public health measures, suggesting that cases of HCV-related HCC will also ultimately decline. However, it may take several decades for this decline to become evident. In the meantime, the number of HCC cases is expected to rise because of the large reservoir of patients with chronic hepatitis C who acquired their infection 20 to 30 years ago, and who are only now beginning to experience complications from this infection. In anticipation of this rise, new and better treatments for HCC are clearly needed.

### Table 8.1.

#### Annual Incidence of Hepatocellular Carcinoma.*

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Untreated Patients</th>
<th>Interferon-Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All†</td>
</tr>
<tr>
<td>F0/F1</td>
<td>0.45 (3/160)</td>
<td>0.08 (2/710)</td>
</tr>
<tr>
<td>F2</td>
<td>1.99 (11/164)</td>
<td>0.54 (16/896)</td>
</tr>
<tr>
<td>F3</td>
<td>5.34 (13/59)</td>
<td>1.95 (38/564)</td>
</tr>
<tr>
<td>F4</td>
<td>7.88 (32/107)</td>
<td>4.16 (33/230)</td>
</tr>
<tr>
<td>Total</td>
<td>3.17 (59/490)</td>
<td>1.10 (89/2400)</td>
</tr>
</tbody>
</table>

*Calculated by using the person-years method.

†Includes 43 interferon-treated patients whose response to interferon was not determined.

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REFERENCES

Therapy for hepatitis C virus (HCV) infection has progressed greatly over the past decade, such that the majority of patients can achieve sustained virologic response (SVR) if dosed properly and if adherence to the optimal regimen is maintained. Factors influencing response to therapy include age, duration of infection, ethnicity, gender, genotype, fibrosis stage, and body weight. Recent interest has focused on how fatty liver may impact response to antiviral therapy, and on strategies for managing side effects in order to promote adherence. Other areas of research interest include strategies for managing hepatitis C in patients who have not responded to current therapies, and improving outcomes in patients with advanced disease. These topics were covered extensively in the preceding chapters of *The Clinician’s Companion VII* and are summarized here.

**Steatohepatitis and Chronic Hepatitis C**

Hepatic steatosis and chronic hepatitis C frequently coexist, and hepatic steatosis likely leads to progression of fibrosis in patients with chronic hepatitis C. The etiopathogenesis involves a complex interplay of both host and virally mediated factors that have only recently begun to be elucidated. Emerging data described in the chapter by Dr. Harrison and Dr. Bacon suggest that host factors such as are seen in patients with nonalcoholic fatty liver disease are more likely to be involved in development of coexistent hepatic steatosis in genotype 1 patients, while genotype 3 patients are more likely to have a virally mediated hepatic steatosis.

In genotype non-3 patients, the presence of coexistent steatosis negatively affects early and sustained response to antiviral therapy for reasons that are not entirely known. Evidence suggests that hepatic steatosis increases fibrosis in patients with chronic hepatitis C. Another contributing factor may be that insulin resistance, whether secondary to the metabolic syndrome or due to a direct viral effect, may alter immune system responses, leading to decreased interferon effectiveness. Obesity may also contribute to decreased bioavailability of interferon. Prospective studies are needed to both confirm this negative association and to determine the potential mechanisms for this altered response to therapy.

**Side Effect Management**

Unfortunately, peginterferon/ribavirin, the standard of care for treatment of HCV infection, has a wide variety of potential adverse events. While the majority of these side effects are mild and tolerable, some are potentially serious. Side effects can reduce quality of life and can limit the effectiveness of treatment if they necessitate dose reduction or discontinuation. Patients should be informed that side effects are expected and should be educated about strategies for side effect management. Adjuvant therapies, such as antidepressants, analgesics, over-the-counter treatments for gastrointestinal side effects, and other available therapies, should be favored over dose reduction or treatment discontinuation whenever feasible, as discussed in the chapter by Dr. Poordad. With careful monitoring and aggressive side effect management, most patients can successfully complete therapy.

Hematologic side effects are among the most common causes of dose reduction or treatment discontinuation. Anemia can substantially reduce quality of life and often results in ribavirin dose reduction. Dr. Younossi reviewed new data showing that the hematopoietic growth factors darbepoetin alfa and epoetin alfa effectively treat anemia, improve health-related quality of life, and help maintain a therapeutic dose of ribavirin. Further investigation into other growth factors for treating neutropenia and thrombocytopenia is needed.

**Management of Hepatitis C in Treatment Nonresponders**

Over half of all patients with chronic HCV infection do not achieve SVR following treatment with peginterferon/ribavirin. There is no standard approach to peginterferon/ribavirin nonresponders, but a longer course of treatment in prior relapsers may be considered. Investigational alternatives include daily consensus interferon/ribavirin, daily consensus interferon/interferon-gamma, and novel agents. Some patients who fail to achieve SVR have an improvement in liver histology that appears to be associated with a marked decline in serum HCV RNA level. As discussed in Dr. Jacobson’s and Dr. Shiffman’s chapters, there is some evidence that continuing interferon long term as maintenance therapy in this select group of patients can continue to suppress serum HCV RNA and hepatic inflammation. It has been hypothesized that this approach may prevent fibrosis progression; reduce the risk of liver cancer, hepatic decompensation, and the need for liver transplantation; and improve mortality in patients with chronic HCV infection. This is currently
being further evaluated in the Hepatitis C Long-term Treatment Against Cirrhosis (HALT-C) and other clinical trials. At the present time, the use of peginterferon maintenance therapy should be considered unproven. However, it is reasonable to utilize this approach in a select group of high-risk patients with advanced bridging fibrosis or stable cirrhosis who have failed to achieve SVR following treatment with peginterferon/ribavirin. The proper dose of peginterferon for maintenance therapy needs to be identified.

Future Therapies

New therapies for hepatitis C are still needed in order to provide further opportunities for SVR to peginterferon/ribavirin nonresponders as well as those who are not candidates for or unable to tolerate peginterferon/ribavirin. The ideal therapy for any disease should be highly effective, orally bioavailable, have a minimal side-effect profile, and be cost-effective and appropriate for the majority of patients. Despite the absence of a suitable small animal model to address new drug development in hepatitis C, recent advances in our understanding of the replication cycle of HCV, improved structural definitions of key components of the viral polyprotein, and crystallography techniques have enhanced the prospects for development of newer therapies. Strategies to enhance response to current therapies include the development of novel interferons and delivery systems, nucleoside analogues that produce less hemolysis than ribavirin, IMPDH inhibitors, and other immunomodulators that are currently being evaluated in clinical trials as adjunctive therapy to interferon-based regimens. Compounds in preclinical or early-phase human trials include small molecules that inhibit virus-specific enzymes (such as the nonstructural serine proteases, RNA polymerase, and helicase), or those that prevent translation initiation (such as antisense molecules and ribozymes). Antifibrotic strategies are also being actively developed in an attempt to prevent disease progression in those patients in whom viral RNA cannot be eradicated. The advent of these newer compounds represents an exciting phase in HCV treatment, but their safety and efficacy compared with currently available treatments need to be established. Hence, most of these newer therapies are unlikely to be available for routine use in the next few years.

Liver Transplantation

Liver transplantation is the standard of care in the management of patients with complications of end-stage liver disease. Short- and medium-term outcomes with transplantation are excellent, although recurrence of the primary disease, and complications of immunosuppressive therapy affect long-term survival.

The major problem with liver transplantation today is the lack of availability of suitable organs, as noted in Dr. Wright’s chapter. Four times as many individuals await transplantation than undergo liver transplantation each year. In 2002, the United Network for Organ Sharing (UNOS) introduced the Model for End-stage Liver Disease, which is based on “objective” prognostic markers, in order to make liver transplantation available to those at greatest risk of dying without transplantation. Live-donor liver transplantation (LDLT) has been used, initially for pediatric and more recently for adult recipients, in order to increase the number of patients undergoing liver transplantation annually, although the number of persons undergoing LDLT is relatively small.

Recurrent hepatitis C posttransplantation remains a major problem in most transplant centers. Hepatitis C is the leading indication for liver transplantation; yet recurrence of infection, which is universal, may result in progressive disease of the allograft leading to premature graft failure. While peginterferon/ribavirin therapy offers some promise in the treatment of established disease of the graft, toxicities are greater and efficacy lower than in nonimmunosuppressed patients with chronic HCV disease. New effective hepatitis C antivirals are eagerly awaited. Improvement in the management of patients undergoing liver transplantation will depend on the development of immunosuppressive drugs with fewer toxicities, increase in the number of available donors, and improvement in the management of recurrent diseases in the graft. Ultimately, identification of patients with liver disease before they develop complications, and effective treatment of the disease at that time, will decrease the overall need for liver transplantation and its attendant complications.

Hepatitis C and Hepatocellular Carcinoma

Chronic hepatitis C is a common risk factor for the development of hepatocellular carcinoma (HCC). Although the mechanism by which HCV infection results in HCC is not known, changes associated with cirrhosis play an important role as almost all patients with HCV-related HCC have underlying cirrhosis. Several co-factors have been identified that may interact with HCV, including excessive alcohol consumption, coinfection with hepatitis B virus, and possibly diabetes or nonalcoholic fatty liver disease.

Screening and surveillance for HCC should be directed toward patients with chronic hepatitis C and cirrhosis. Screening commonly consists of serial ultrasound examination every 6 to 12 months, although there is no direct evidence that this affects patient survival. There is evidence from retrospective studies that antiviral therapy with interferon reduces the risk of HCC in hepatitis C patients, although the routine use
of long-term suppressive therapy of hepatitis C with interferon should await the completion of ongoing prospective studies.

**Conclusion**

Considerable enhancements have been made in the management of hepatitis C recently, and we now have better strategies for making treatment more tolerable by reducing side effects. Promoting adherence betters the chances of SVR. However, there are still a number of challenges that remain to be addressed in the management of hepatitis C. New therapies are needed to address the growing population of nonresponders and to prevent progression of fibrosis. Until such therapies are available, the need for liver transplants will continue to rise, outpacing supply. Ongoing investigations into new therapies and strategies for hepatitis management are promising, and further advances in care can be expected in the years to come.
Drugs or Investigational Agents Mentioned in this Publication

In accordance with the ACCME Essential Areas and Policies regarding commercial support, the audience is advised that this continuing medical education activity may contain reference(s) to unlabeled or unapproved use of drugs or devices.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Names(s)</th>
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</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Tylenol®</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Hepsera™</td>
</tr>
<tr>
<td>Albumin-interferon alpha</td>
<td>Albufera™</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Symmetrel®</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Abelcor®, AmBisome®, Amphotec®</td>
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<td>Antilymphocyte globulin</td>
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<tr>
<td>Azathioprine</td>
<td>Azasyn™, Imuran™</td>
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<td>Basiliximab</td>
<td>Simulect®</td>
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<td>BILN 2061</td>
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<td>Cyclosporine</td>
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<td>Darbepoetin alfa</td>
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<tr>
<td>Epoetin alfa</td>
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<td>Halofuginone</td>
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<td>HCV-866</td>
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<tr>
<td>HCV vaccine</td>
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<tr>
<td>HCV vaccine/MSF9</td>
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</tr>
<tr>
<td>Hepatitis B immune globulin</td>
<td>BayHep B®, Naïf-HBV™</td>
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<tr>
<td>Hepatitis C immune globulin</td>
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<td>Histamine dihydrochloride</td>
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<td>IDN-6356</td>
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<td>Imiquimod</td>
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<td>INNO 101</td>
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<td>Interferon alfa-2b</td>
<td>Intron® A</td>
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<tr>
<td>Interferon gamma-1b</td>
<td>Actimmune®</td>
</tr>
<tr>
<td>Interferon omega</td>
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</table>

Generic Name | Trade Names(s)

Isoniazide (ANA245) | (Trade name(s) not available)
BIL-18403 | (Trade name(s) not available)
JXK-003 | (Trade name(s) not available)
Lamivudine | Epivir®
L-isomer of ribavirin | Levovirin™
Mestinopodil (VX-497) | (Trade name(s) not available)
Methadone | Dolophine®, Methadone®
Methylphenidate | Concerta®, Metadate®, methylphenidate, Ritalin®
Modafinil | Provigil®
Muromonab-CD3 | Orthoclone OKT® 3
Mycophenolate Mofetil | CellCept®
NM107 | (Trade name(s) not available)
NM283 | (Trade name(s) not available)
Oprelvekin | Neumega®
Pegfilgrastim | Neulasta®
Peginterferon alfa-2a | Pegaspary®, Peginterferon alfa-2b | Peg-Infon®
PEG-Aldalcon-1 | Pegylated interferon alfacon-1 |
Prednisone | Deltasone®
R803 | (Trade name(s) not available)
Resiquimod | (Trade name(s) not available)
Ribavirin | (Trade name(s) not available)
Ripamune | Copegus®, Rebetol®
1,2,4-triazole-3-carboxamidine | Viramidine™
Ribavirin | (Trade name(s) not available)
Ribostemine | (Trade name(s) not available)
Stromifur, rapamycin | Rapamune®
Tacrolimus | Prograf®
Temazepam | Restoril®
Thymosin alpha-1 | Zadaxus®
Trazodone | Desyrel®
UT-231-B | (Trade name(s) not available)
Valganciclovir | Valcyte®
XTL002 | Hepeg™ C
Zaleplon | Sonata®
Zolpidem | Ambien®
CME Instructions

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Name ___________________________________________ Degrees/Credentials ________________________________

Mailing Address ________________________________________________________________________________________

City _______________________________   State  __________   ZIP _____________________________________________

Phone _______________________________________________  Fax _____________________________________________

E-mail ________________________________________________________________________________________________

1. Hepatic steatosis occurs in <10% of patients with chronic hepatitis C (CHC). ❑ ❑
2. Similar to patients with nonalcoholic fatty liver disease (NAFLD), genotype 1 CHC patients with hepatic steatosis are often obese, and have diabetes mellitus, hypertension, visceral adiposity, and insulin resistance. ❑ ❑
3. Virally mediated steatosis is most likely to be found in genotype 1. ❑ ❑
4. Obesity, and thus insulin resistance, may decrease the effectiveness of antiviral therapy via a process that involves the satiety hormone, leptin. ❑ ❑
5. Peak side effects of peginterferon (PEG IFN) alfa-2a are often noted in the second to third month of therapy, whereas they tend to occur earlier with PEG IFN alfa-2b. ❑ ❑
6. Modafinil, which has been used off-label to treat fatigue in hepatitis C virus (HCV) infection, promotes wakefulness and locomotor activity. ❑ ❑
7. The overall incidence of new depression during treatment with interferon (IFN) is 80% to 90%. ❑ ❑
8. Anxiety and irritability are often the only signs of depression in men on IFN therapy. ❑ ❑
9. The presence of mania requires immediate IFN discontinuation and psychiatric assessment. ❑ ❑
10. Mild anemia (Hgb < 12 g/dL) is observed in almost half of all patients on IFN/ribavirin (RBV) combination therapy. ❑ ❑
11. Anemia was found to have no impact on occupational functioning in assessments of health-related quality of life. ❑ ❑
12. In a randomized, placebo-controlled trial, epoetin alfa improved health-related quality of life scores among anemic HCV-infected patients receiving IFN alfa and RBV or PEG IFN alfa and RBV. ❑ ❑
<table>
<thead>
<tr>
<th>True</th>
<th>False</th>
</tr>
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<tbody>
<tr>
<td>13. Data from two recent clinical trials indicate that darbepoetin alfa administered at reduced frequency is as safe and effective as epoetin in patients with renal disease who are dialysis-dependent.</td>
<td>❑</td>
</tr>
<tr>
<td>14. Serious bacterial infections commonly occur with IFN-related neutropenia.</td>
<td>❑</td>
</tr>
<tr>
<td>15. The HALT-C trial confirmed that reduction of RBV dose during the first 20 weeks of therapy negatively affects response.</td>
<td>❑</td>
</tr>
<tr>
<td>16. Relapsers to IFN/RBV have higher sustained virologic response (SVR) rates to PEG IFN/RBV than prior nonresponders to IFN/RBV.</td>
<td>❑</td>
</tr>
<tr>
<td>17. A marked reduction in viral load in nonresponders to prior IFN/RBV therapy helps predict response to PEG IFN/RBV retreatment.</td>
<td>❑</td>
</tr>
<tr>
<td>18. Relapse rates in treatment nonresponders are similar to relapse rates in treatment-naive patients with PEG IFN/RBV.</td>
<td>❑</td>
</tr>
<tr>
<td>19. Maintenance therapy with PEG IFN is currently an approved application of antiviral therapy based on published results of multicenter studies.</td>
<td>❑</td>
</tr>
<tr>
<td>20. Histologic improvement during or following IFN therapy is directly related to reduction and/or eradication of HCV RNA, as well as reduction of hepatic inflammation.</td>
<td>❑</td>
</tr>
<tr>
<td>21. Most data accumulated to date point to the fact that histologic improvement during or following therapy is due to the direct anti-inflammatory and/or antifibrotic effects of IFN/RBV.</td>
<td>❑</td>
</tr>
<tr>
<td>22. PEG IFN maintenance therapy should be used only in patients with advanced fibrosis or cirrhosis and preserved hepatic function.</td>
<td>❑</td>
</tr>
<tr>
<td>23. Incidence rates of hepatocellular carcinoma (HCC) are lowest in southern Africa.</td>
<td>❑</td>
</tr>
<tr>
<td>24. Consumption of excessive alcohol is well-known to promote the progression of hepatic fibrosis due to hepatitis C and is considered the major cause of HCC in both developing and developed countries.</td>
<td>❑</td>
</tr>
<tr>
<td>25. Surveillance for HCC is recommended in HCV-infected patients only if they have cirrhosis, since patients without cirrhosis rarely develop HCC.</td>
<td>❑</td>
</tr>
<tr>
<td>26. Patient survival following alcohol ablation of HCC is significantly lower than that after hepatic resection for the same tumor.</td>
<td>❑</td>
</tr>
<tr>
<td>27. Data from several large retrospective studies suggest that antiviral therapy of chronic hepatitis C with IFN alfa reduces the risk of HCC.</td>
<td>❑</td>
</tr>
<tr>
<td>28. Attempts to develop an oral IFN have been hampered because of the difficulty of delivering effective doses of IFN to the liver.</td>
<td>❑</td>
</tr>
<tr>
<td>29. Levovirin, the L-sugar isomer of RBV, inhibits IMPDH and accumulates in erythrocytes.</td>
<td>❑</td>
</tr>
<tr>
<td>30. A single drug that inhibits viral enzyme production will suppress virus for the duration of therapy, but eventually promote development of resistance to that drug.</td>
<td>❑</td>
</tr>
<tr>
<td>31. Currently, hepatitis B virus infection with active viral replication and HIV infection are absolute contraindications to liver transplantation.</td>
<td>❑</td>
</tr>
<tr>
<td>32. In adult-to-child living-donor liver transplant (LDLT), the child receives the larger right lobe of the adult donor’s liver.</td>
<td>❑</td>
</tr>
<tr>
<td>33. HCV-infected recipients are at high risk of progressive HCV posttransplantation following transplantation with organs from older donors and donors with hepatic steatosis.</td>
<td>❑</td>
</tr>
</tbody>
</table>
CME Evaluation Survey
THE CLINICIAN’S COMPANION VII: EXPERT PERSPECTIVES ON CONTEMPORARY CLINICAL ISSUES IN HEPATITIS C

Name __________________________________________ Degrees/Credentials ______________________________

Address _______________________________________________________________________________________________

City __________________________________________ State ___________________ ZIP ___________________

Instructions: Please complete this survey, along with the CME Posttest, and mail or fax (both sides) to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424; fax: 973-890-8866. We cannot issue CME certificates of credit without both documents.

1. Please rate the extent to which you achieved the learning objectives:
   - Discuss advances and new directions in HCV diagnosis, monitoring, and treatment.
     - Excellent □ Very Good □ Good □ Satisfactory □ Poor □
   - Use diagnostic procedures, including various HCV assays and tests to assess the degree of liver fibrosis, in a timely fashion and in accordance with the latest guidelines to identify infected individuals and monitor treatment response.
     - Excellent □ Very Good □ Good □ Satisfactory □ Poor □
   - Formulate effective treatment strategies for patients with chronic HCV infection.
     - Excellent □ Very Good □ Good □ Satisfactory □ Poor □
   - Promote adherence to anti-HCV therapy by emphasis on patient education and the management of side effects.
     - Excellent □ Very Good □ Good □ Satisfactory □ Poor □
   - Address the unique needs of specific patient groups, including HIV/HCV-coinfected patients, patients with advanced kidney or liver disease, nonresponders to first-line therapy, diabetics, and others.
     - Excellent □ Very Good □ Good □ Satisfactory □ Poor □
   - Provide appropriate treatment and monitoring to patients with advanced liver disease.
     - Excellent □ Very Good □ Good □ Satisfactory □ Poor □
   - Develop an overall care plan for patients with advanced HCV-related liver disease who require liver transplantation.
     - Excellent □ Very Good □ Good □ Satisfactory □ Poor □

2. Please rate the extent to which this activity achieved the stated goal: The goal of Clinician’s Companion VII: Expert Perspectives on Contemporary Clinical Issues in Hepatitis C is to provide clinicians with a solid foundation of knowledge and practical clinical skills to apply in practice, and the latest diagnostic, monitoring, and treatment strategies.
   - Excellent □ Very Good □ Good □ Satisfactory □ Poor □

3. Please rate the overall value of this enduring material.
   - Strongly Agree □ Agree □ Disagree □ Strongly Disagree □

4. Course was free from commercial bias:
   If you “Disagree” or “Strongly Disagree,” why? ....................................................................................................................
   - Strongly Agree □ Agree □ Disagree □ Strongly Disagree □

5. Course was objective and independent:
   - Strongly Agree □ Agree □ Disagree □ Strongly Disagree □
6. Please rate the level of the material presented:

   [ ] Just Right  [ ] Too Advanced  [ ] Too Basic

7. Please list any changes in your practice that you would consider making as a result of participating in this activity:

   ...............................................................................................................................................................................................
   ...............................................................................................................................................................................................
   ...............................................................................................................................................................................................

8. Please rate your interest in self-directed or distance learning in the following formats:

   Very Interested  Moderately Interested  Not Interested

   a. Audioconference [ ] [ ] [ ]
   b. Videoconference [ ] [ ] [ ]
   c. Enduring materials (audio CDs, videotapes, monographs) [ ] [ ] [ ]
   d. Internet (online discussions with experts, educational activities) [ ] [ ] [ ]
   e. Multimedia (online, CD-ROM) [ ] [ ] [ ]

9. Please tell us exactly how long it took you to complete this course (circle hours):

   Hours: 1 1.25 1.5 1.75 2 2.25 2.5 2.75 3

10. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

   ...............................................................................................................................................................................................
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11. Follow-up:

    As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:

    [ ] Yes, I would be interested in participating in a follow-up survey.
    [ ] No, I’m not interested in participating in a follow-up survey.

    Additional comments about this activity: .................................................................................................................................................................
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Thank you for your participation.