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OPTIMIZING ADHERENCE TO
THERAPY IN HEPATITIS C:
CHALLENGES AND EMERGING STRATEGIES

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OPTIMIZING ADHERENCE TO THERAPY IN HEPATITIS C: CHALLENGES AND EMERGING STRATEGIES

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Foreword

Why a supplement on chronic hepatitis C, and why now? The answer boils down to two simple issues: hepatitis C is an increasingly relevant disease, and its management has been remarkably dynamic in recent years.

The disease's relevance stems from its prevalence and the potential for serious sequelae. Chronic infection with hepatitis C virus (HCV) remains one of the most common causes of liver disease worldwide and the most frequent indication for liver transplantation in the United States. Moreover, morbidity and mortality related to hepatitis C are projected to increase substantially over the next 2 decades.

But the most exciting story about this disease in recent years has been its management. Over the past decade, the treatment of chronic hepatitis C has evolved from thrice-weekly injections of interferon alfa monotherapy, which yielded sustained virologic response rates of less than 15%, to a combination of weekly injections of pegylated interferon alfa and daily ribavirin therapy, which produces sustained virologic response rates of approximately 55%.

Along the route to this progress we've learned many interesting lessons to further refine patient management. For example, we've discovered that a HCV genotype of 2 or 3 is the pretreatment viral factor that has consistently been associated with higher response rates to antiviral therapy. Additionally, the lack of an early virologic response (at 12 weeks) is generally an excellent predictor of nonresponse to antiviral therapy.

Recent years have also shown that delivering the optimal dose of antiviral therapy is associated with improved response rates. Delivering this optimal dose is especially important early in the course of antiviral therapy (during the initial 12 weeks), and its importance has been established most convincingly with regard to the dosing of ribavirin in patients infected with HCV genotype 1. Unfortunately, however, delivering this optimal dose of antiviral therapy has

also been associated with a number of side effects related to both interferon/peginterferon and ribavirin. These include development of neutropenia, anemia, and thrombocytopenia as well as interferon-induced neuropsychiatric side effects, a nonspecific flulike syndrome, dry cough, dyspnea, and itching.

In this supplement, our collection of internationally renowned hepatologists provide an up-to-date review of strategies for managing these side effects and guidance for enhancing adherence to the optimal antiviral regimen for chronic hepatitis C. These "adjuvant" strategies include the use of hematopoietic growth factors (epoetin alfa and darbepoetin alfa) for ribavirin-induced anemia as well as filgrastim for managing severe interferon-related neutropenia. Also discussed are strategies for addressing the neuropsychiatric side effects of interferon, including approaches to psychiatric assessment, monitoring, and treatment. The supplement's final article focuses on physician extenders and their increasingly crucial role in the management of HCV-infected patients, especially for managing the side effects of antiviral therapy.

We hope that presenting a number of strategies to improve patients' health-related quality of life (eg, treatment of anemia, patient education, simple interventions for side-effect management) may serve to improve adherence to treatment. Such an improvement in adherence may potentially increase the likelihood that antiviral therapy will be efficacious in a given patient. Regardless of what the next generation of antiviral therapy for chronic hepatitis C will be, strategies to improve adherence will remain helpful in optimizing outcomes for patients infected with HCV.

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The evolving treatment of chronic hepatitis C: Where we stand a decade out

SHERIF SAADEH, MD, AND GARY L. DAVIS, MD

■ ABSTRACT

The treatment of hepatitis C has evolved rapidly since the identification of the hepatitis C virus (HCV) in 1989. Since the first accepted therapy for HCV infection, recombinant interferon, received marketing approval a little more than a decade ago, it has come to be used in combination with ribavirin for improved rates of sustained virologic response. Recently, pegylated versions of interferon have been developed for use with ribavirin, offering pharmacokinetic advantages and further improvements in response rates over conventional interferon. This article briefly reviews how these evolving regimens for HCV infection have addressed the subtle and singular characteristics of this challenging virus.

Effective treatment for infection with the hepatitis C virus (HCV) was first described more than a decade ago and has evolved rapidly since. However, to understand the evolution of treatment for hepatitis C, we must look back much further. Critical milestones that cleared the way for the development of management and treatment strategies for hepatitis C include:

- The recognition that different hepatitis viruses exist, and their subsequent identification and characterization
- Growth in knowledge of the mechanisms by which

viruses, and particularly HCV, replicate and cause cell injury

- The explosion in drug development technology driven by modern molecular biology techniques and the race to identify antiviral agents with activity against the human immunodeficiency virus (HIV).

This short review surveys key developments in the discovery of HCV and in our evolving treatment approaches to HCV infection.

■ EPIDEMIOLOGY AND IMPACT OF HEPATITIS C

Infection with HCV is a major cause of chronic liver disease worldwide, affecting 175 million people. In the United States, it is estimated that 2.7 to 4 million people are infected with the virus (the former estimate is based on the Third National Health and Nutrition Examination Survey, which excluded several high-risk groups in the population). On average, up to 80% of acutely infected patients go on to develop chronic infection. At least 20% to 25% of these patients will eventually develop cirrhosis and be at risk for its complications. The sequelae of HCV-induced chronic liver disease account for more than 12,000 deaths annually and are the leading indications for liver transplantation in the United States. HCV-related morbidity and mortality are expected to increase markedly over the next 2 decades.¹

■ DISCOVERY AND CHARACTERIZATION OF HCV

The infectious nature of yellow jaundice was recognized in the 8th century AD. Epidemic jaundice was common, and many or most cases were probably due to enteric transmission of what is now known as the hepatitis A virus. Percutaneous transmission of the disease was not recognized until the advent of inoculation for smallpox vaccination in the 1880s, and many reports of jaundice in patients receiving vaccines or injections for diabetes or syphilis followed in the early 20th century. The first association of blood transfusion

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with the development of hepatitis was reported in 1943. Landmark studies by Krugman and colleagues at the Willowbrook State School in New York established the transmissibility of hepatitis by human plasma and confirmed long-standing clinical observations that both parenteral (“serum hepatitis”) and enteric (“infectious hepatitis”) transmission could occur.²

Frustrating and largely unsuccessful efforts to identify the specific agents responsible for hepatitis continued over several decades. A serologic marker for hepatitis B virus was identified by Blumberg in 1965, but its association with the parenterally transmitted entity known as serum hepatitis was not recognized until 2 years later.² The specific viral agents responsible for hepatitis B and A came to be recognized over the next few years.² These discoveries were landmark breakthroughs, but it was soon apparent that most cases of hepatitis could not be explained by either the hepatitis A or the hepatitis B virus. The entity of “non-A, non-B hepatitis” was formally christened in the mid-1970s.²

An infectious agent was suspected as the cause of this disease entity since it was parenterally transmissible to chimpanzees and humans by blood transfusion, but identification of the agent proved elusive for many years. Bradley and colleagues at the Centers for Disease Control and Prevention characterized the biochemical nature of the infectious agent, but conventional virologic and immunologic techniques of the time failed to isolate it. Working independently, scientists at Chiron Corporation and scientists in Japan used then-recent molecular biology techniques in attempts to isolate what Bradley’s work had suggested might be an RNA virus resembling the Flaviviridae. The identified peptides cross-reacted with sera from patients with non-A, non-B hepatitis and from experimentally infected chimpanzees. Extrapolation from clones with overlapping regions of the viral complementary DNA subsequently allowed investigators to establish the entire viral genome. This breakthrough led to an explosion of research on this viral agent, now designated “hepatitis C virus,” and its disease, now called hepatitis C.³

A virus with vigorous replication

HCV was subsequently characterized as a flavivirus-like RNA virus, as originally suspected, and over time its replicative cycle has been largely characterized, even though HCV has proven difficult to grow efficiently in cell culture and there are no widely available animal models.

The virus replicates at a very high rate, producing

more than 10^{12} viral copies per day, but the viral half-life is short, resulting in rapid turnover.⁴ Moreover, like other RNA viruses, HCV uses the viral error-prone RNA polymerase for replication, which results in the production of innumerable random uncorrectable nucleotide errors and a heterogeneous virus population that promotes genetic evolution. Today, isolates of the virus are distinguished by their genetic relatedness (genotype) as determined by phylogenetic tree analysis. Six major genotypes and more than 100 subtypes have been defined. We now know that these genotypes have subtle differences in replicative and host interactions, and therefore have important therapeutic implications, as discussed below.

■ **PATHOGENESIS OF HCV-RELATED LIVER DISEASE**

Multiple factors influence the interaction between HCV and the infected host, resulting in an extremely individual and variable disease presentation. Although viral replication is critical in the development of liver disease from HCV infection, the virus does not appear to be directly cytopathic to liver cells under most circumstances. For example, an exception may be the unique and often lethal cytopathic type of liver injury observed in some transplant recipients with extremely high virus levels. Viral factors such as genotype, the presence and diversity of viral quasi-species, and the level of replication appear unrelated to disease severity in most cases. Rather, it appears that host factors, particularly the cellular immune response, influence the course of the disease. Unfortunately, good characterization of the role of the host immune response in the pathogenesis of liver disease has been hampered by the lack of a small animal model or an efficient cell culture model.

■ **TREATMENT OF HCV-RELATED LIVER DISEASE**

There were only a few forays into treatment of chronic non-A, non-B hepatitis before the identification of HCV in 1989. Corticosteroids were commonly used to treat chronic hepatitis before viral etiologies were recognized. Prednisone often reduced serum aminotransferase levels, but normalization of liver enzyme levels or a significant improvement in disease course was not noted. Acyclovir was studied in a small pilot trial and did not change the aminotransferase levels.

Interferon monotherapy

Interferons were first described in 1957 by Isaacs and Lindeman and were so named because of their ability to “interfere on” viral replication. Interferons are nat-

urally occurring glycoproteins that are produced *in vivo* by leukocytes in response to viral infection. Pharmacologic doses of interferons were first produced by stimulation of cultures of buffy-coat lymphocytes collected from blood donors. Later, interferons were produced commercially from cell lines or the much more efficient recombinant technology. Most commercially available interferons today are recombinantly produced.

Interferons inhibit the replication of many viruses, including hepatitis viruses, through a variety of mechanisms, including direct antiviral action (inhibition of virus attachment and uncoating, induction of intracellular proteins and ribonucleases) and by amplification of specific (cytotoxic T lymphocyte) and nonspecific (natural killer cell) immune responses.⁵ Although interferon alfa ("interferon" hereafter) suppresses the level of HCV replication, it is generally believed that HCV clearance is mediated at least in part by enhancement by interferon of the host immune response to the virus.

In the late 1980s, interferons became the first agents to be systematically studied for treatment of what was then called chronic non-A, non-B hepatitis.⁶ Those early studies demonstrated that a 6-month course of recombinant interferon normalized serum alanine aminotransferase (ALT) levels in nearly half of treated patients (47% vs 2% in untreated controls) and reduced hepatic inflammation in most treated patients (67% vs 15% in untreated controls).⁷ When molecular tools later emerged to detect the etiologic agent of the disease, analysis of stored samples showed a loss of detectable HCV RNA in most of the patients who had achieved a biochemical response during treatment.

Unfortunately, responses to the short courses of interferon initially employed were often transient, and relapse was common when treatment was stopped. Sustained normalization of ALT levels was demonstrated in about 20% of cases, and sustained loss of virus occurred in only 8% to 11%.² However, no other treatments were available for patients with chronic hepatitis C. Thus, despite the meager rate of permanent viral and biochemical response to a 6-month course of therapy, recombinant interferon was approved by the US Food and Drug Administration in 1991.

Extending the treatment course from 6 to 12 months did not improve the proportion of patients with normalization of serum ALT, but fewer patients relapsed after treatment was stopped, so that sustained improvement was achieved in 38% of patients given a 12-month course compared with 22% of those given a 6-month course.⁷ Sustained loss of virus persisting for

at least 6 months after completion of therapy, hereafter referred to as sustained virologic response (SVR), was observed in up to 30% of cases, but averaged about 16%.^{2,8} Furthermore, histologic improvement was seen in most patients treated for 1 year. Other regimen variations, including daily dosing, escalating doses, and high-dose induction therapy, were also studied, but these did not increase response rates compared with conventional three-times-weekly interferon monotherapy. Furthermore, higher-dose regimens were poorly tolerated.

Ribavirin monotherapy

Ribavirin is a nucleoside analog with a structure similar to azathioprine. It has been known for 30 years to have antiviral activity against several viruses. Ribavirin is well absorbed in the proximal small intestine and, upon entering cells, is phosphorylated to ribavirin triphosphate, which impedes transportation across cell membranes unless it can be dephosphorylated. At an oral dosage of 600 mg twice daily, steady state is reached after approximately 4 weeks.

Ribavirin's mechanism of action against HCV is not known. Early studies using oral ribavirin monotherapy, given at a dosage of 600 mg twice daily, found that serum ALT levels fell to within the normal range in 40% of treated patients, and this was associated with a reduction in hepatic inflammation.⁹ Moreover, fatigue improved despite the hemolytic anemia and the mean fall in hemoglobin of more than 2 g/dL that occurred with treatment. Virus levels, however, did not change during treatment.⁹ Although these studies did not demonstrate antiviral efficacy, the results were intriguing enough to encourage further investigation, including use in combination with interferon.

Combination therapy with interferon and ribavirin

The combination of oral ribavirin with recombinant interferon given three times per week led to significant improvement in the SVR rate compared with interferon alone. Reports from studies of treatment-naïve patients demonstrated SVR rates of 30% after 24 weeks of combination therapy compared with 6% after 24 weeks of interferon monotherapy.^{8,10} A 48-week treatment course achieved SVR in 38% of treatment-naïve patients receiving combination therapy, compared with 13% of those receiving interferon monotherapy.⁸ The benefit of extending therapy to 48 weeks was confined to patients infected with HCV genotype 1; in these patients, the SVR rate was 28% with 48 weeks of therapy vs 16% with 24 weeks. Extending therapy conferred no benefit in patients

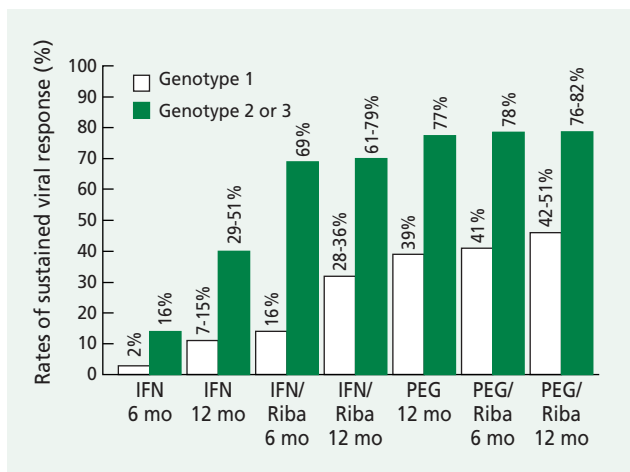


FIGURE 1. Rates of sustained virologic response, presented by patients' HCV genotype, to various interferon-based regimens over the last 15 years (IFN = interferon; PEG = pegylated interferon; Riba = ribavirin). Rates presented as ranges represent data from more than one trial (bar heights represent the mean of the range in these cases).

with genotypes 2 or 3 (SVR of 66% with 48 weeks vs 69% with 24 weeks).

Combination therapy was also beneficial in patients who had a suboptimal response to interferon alone. In one major trial, patients who relapsed following interferon monotherapy achieved higher SVR rates when retreated with combination therapy than with interferon monotherapy (49% vs 5%).¹¹ Additionally, SVR has been achieved in 10% to 25% of nonresponders to IFN monotherapy who have been retreated with combination therapy.¹²

The FDA approved the combination of oral ribavirin and interferon in 1998 for the treatment of patients with chronic HCV infection who relapsed within 1 year of initial therapy. Data showing clear improvement of outcomes in treatment-naïve patients led to extension of the indication later that year to include previously untreated patients as well.

Pegylated interferons

One reason for the limited response to interferon is its short half-life (2 to 5 hours), which leads to wide fluctuations in plasma concentrations of the drug during treatment. Given the vigorous replication kinetics of HCV described above, it was expected that intermittent dosing of interferon would not be optimal for viral suppression.

Pegylation of interferon, in which polyethylene glycol (PEG) is covalently attached to the parent drug, reduces renal clearance, prolongs the plasma half-life, and increases drug exposure over time, per-

mitting once-weekly dosing. Two pegylated interferon products—peginterferon alfa-2a and peginterferon alfa-2b—are now commercially available for human use. Despite differences in the pharmacokinetic properties of these two pegylated compounds, both are dosed once weekly, with drug levels still detectable before the next dose, and they are associated with similar treatment responses.

Combination of pegylated interferon and ribavirin

The combination of pegylated interferon and ribavirin is easier for patients to use, improves SVR in most groups of previously untreated patients, and is the current standard of care for patients with chronic hepatitis C.

Two clinical studies compared 1 year of therapy with either pegylated interferon and ribavirin or non-pegylated interferon and ribavirin.^{13,14} Despite differences between these trials in study design, the pegylated interferon agents used, the ribavirin doses used, and patient characteristics, the outcomes were remarkably similar: SVR was achieved in 54% to 56% of treated patients (41% to 42% for patients with genotype 1 and 66% to 75% for those with genotype 2 or 3).

Optimal treatment durations and ribavirin doses have recently been more clearly defined for these combination regimens. For patients with HCV genotype 1, the optimal course is 1 year of therapy with pegylated interferon plus ribavirin given at a dosage of 1,000 mg/d for those with body weight less than 75 kg and 1,200 mg/d for those weighing more than 75 kg.¹⁵ However, for patients with HCV genotype 2 or 3, response is just as good with only 6 months of combination therapy with pegylated interferon and ribavirin 800 mg/d as it is with a longer treatment course and higher ribavirin doses. Thus, determining the viral genotype before treatment remains a critical step in selecting the best treatment regimen.

Optimal dosing and treatment duration with this combination regimen are discussed in greater detail in the next article in this supplement.

Clinical benefits of sustained virologic response

Sustained virologic response to interferon-based treatment is durable, with late relapse or reinfection occurring in only about 3% of responders.¹⁶ SVR is further associated with a reduction of hepatic inflammation on liver biopsy, often to normal, and stabilization of hepatic fibrosis, with actual regression in more than half of cases.¹⁷ It is reasonable to assume that these short-term benefits translate into a reduction in

morbidity and mortality. In addition, response to therapy is associated with an improvement in health-related quality of life.

THE NEXT 10 YEARS: REMAINING CHALLENGES

Over the last decade, our knowledge and treatment of chronic hepatitis C have evolved considerably. SVR remains the goal of treatment, as it connotes durable virus eradication, histologic improvement, and improved quality of life. While initial treatment, consisting of nonpegylated interferon alone for 6 months, was associated with disappointing SVR rates of less than 10%, the current standard of care, pegylated interferon plus ribavirin, is associated with HCV eradication in more than half of treated patients (Figure 1).

Despite our remarkable progress, several obstacles to improving treatment results remain. As detailed later in this supplement, many patients are unable to begin or tolerate interferon-based therapy because of medical contraindications, cytopenia, or neuropsychiatric symptoms. Other groups respond less well to treatment, including those with genotype 1 and high virus levels, coinfection with HIV or hepatitis B virus, advanced hepatic decompensation, obesity, or African American ethnicity. Clearly, there is considerable room for improvement in our treatment options. More tolerable therapeutic regimens must be found and antiviral agents that target the replicative machinery of the virus must be identified as a way to treat patients who cannot receive or tolerate interferon-based regimens.

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Initial treatment for chronic hepatitis C: Current therapies and their optimal dosing and duration

KEYUR PATEL, MD, AND JOHN G. MCHUTCHISON, MD

■ ABSTRACT

The main treatment goal in patients with chronic hepatitis C virus (HCV) infection is the prevention of progressive hepatic fibrosis by eradicating serum and intrahepatic virus. The current standard of care in previously untreated patients with chronic hepatitis C is combination therapy with pegylated interferon alfa and ribavirin. The duration of therapy and the dose of ribavirin should be determined according to the patient's HCV genotype. Adherence to the full dose of therapy for the prescribed treatment duration enhances the likelihood of sustained virologic response. Early virologic response is a good predictor of eventual sustained response for patients with HCV genotype 1 infection. Despite important gains in treating chronic hepatitis C, many treatment challenges remain.

The mainstay of therapy for chronic hepatitis C over most of the past decade has been recombinant interferon alfa. In 1998, the addition of the purine nucleoside analog ribavirin to interferon alfa therapy resulted in twofold to threefold higher rates of sustained virologic response (SVR) compared with interferon alfa monotherapy. The advent of the newer pegylated

interferon alfa compounds, also used in combination with ribavirin, has further enhanced response rates, such that more than one half of previously untreated patients can now achieve SVR.

This review outlines the goals of therapy in patients with chronic hepatitis C, examines the available treatment options for previously untreated patients, and examines issues of dosing, treatment duration, and adherence that may optimize virologic response rates.

■ TREATMENT GOALS IN CHRONIC HEPATITIS C

The main goal of treatment in patients with chronic hepatitis C virus (HCV) infection is the prevention of progressive hepatic fibrosis through the eradication of serum and intrahepatic virus. Eradication of HCV is generally evaluated in terms of SVR, which is defined as the absence of serum HCV RNA 24 weeks after the end of treatment (as measured by a sensitive assay with a lower limit of detection of at least 50 IU/mL). The potential long-term benefits of SVR include:

- Normalization of serum alanine aminotransferase levels
- Improvement in hepatic necroinflammation and fibrosis stage in some patients
- Improvement in health-related quality of life
- A probable survival benefit and reduction in the risk of developing hepatocellular carcinoma.

Furthermore, SVR appears to be durable in the vast majority of patients, with fewer than 5% having a virologic relapse over the subsequent 5 to 12 years.¹ However, prospective studies are required to determine whether there is a survival benefit for patients with chronic hepatitis C who achieve SVR.

■ EVOLVING OPTIONS FOR INITIAL TREATMENT

Interferon and ribavirin

In 1998, two pivotal clinical trials led the US Food and Drug Administration (FDA) to approve combination therapy with interferon alfa and ribavirin for

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chronic HCV infection.^{2,3} These two trials included 1,744 previously untreated patients with chronic hepatitis C and compared 24-week and 48-week courses of the following regimens:

- Interferon alfa-2b monotherapy (3 million units three times weekly, given subcutaneously)
- Interferon alfa-2b and ribavirin (1,000 mg/d for patients with body weight ≤ 75 kg, and 1,200 mg/d for those with body weight > 75 kg).

The 48-week combination therapy regimen resulted in significantly enhanced SVR rates compared with 48 weeks of interferon alfa monotherapy: 41% vs 16% (combined rates from the two studies). However, SVR rates among patients receiving 48-week combination therapy were markedly lower for patients with HCV genotype 1 infection (29%) than for patients with other genotypes (62%). Still, SVR rates among patients with genotype 1 were significantly higher if the patient received combination therapy for 48 weeks rather than 24 weeks, whereas the duration of combination therapy did not significantly affect SVR rates among patients with other genotypes.

Results from these two trials led to the recommendation that combination therapy with interferon alfa (3 million units three times weekly, given subcutaneously) and ribavirin (1,000 or 1,200 mg/d orally, based on body weight) be given for 24 weeks to patients with HCV genotype 2 or 3, and for 48 weeks to patients with genotype 1.

The rationale for pegylated interferon

Interferon alfa preparations have a short half-life (6 to 8 hours), which leads to variations in plasma drug concentrations during the recommended thrice-weekly dosing regimen. Pegylated interferons (peginterferons) were developed to improve the pharmacokinetic profile and efficacy of interferon alfa and to provide a more convenient dosing regimen. Pegylation refers to the covalent attachment of an inert, water-soluble polymer of polyethylene glycol (PEG) to the interferon molecule in either a linear chain (peginterferon alfa-2b) or a branched-chain configuration (peginterferon alfa-2a). The resulting larger interferon alfa compounds have improved pharmacokinetic properties and a longer elimination half-life compared with nonpegylated interferons, thus allowing for once-weekly dosing.

Pegylated interferon and ribavirin: How the clinical trials refined dosing and use

Three large trials⁴⁻⁶ have evaluated virologic response to peginterferon and ribavirin in previously untreated patients with chronic hepatitis C.

The first trial⁴ included 1,530 patients and compared 48 weeks of therapy with the following combination regimens:

- Peginterferon alfa-2b 1.5 µg/kg/wk and ribavirin 800 mg/d (higher-dose peginterferon)
- Peginterferon alfa-2b 0.5 µg/kg/wk and ribavirin 1,000 or 1,200 mg/d, based on body weight (lower-dose peginterferon)
- Nonpegylated interferon alfa-2b (3 million units three times weekly) and ribavirin (1,000 or 1,200 mg/d, based on body weight).

Patients who received the higher-dose peginterferon combination regimen had overall SVR rates of 54%, compared with 47% for the other two treatment arms. Patients with HCV genotype 1 had an SVR rate of 42% if they received this higher-dose peginterferon combination regimen, whereas SVR rates were approximately 80% for patients with genotype 2 or 3 irrespective of the treatment regimen. The following pretreatment variables were associated with a higher likelihood of SVR: an HCV genotype other than genotype 1, lower HCV RNA levels, absence of significant fibrosis, younger age, and lower body weight.

In this study, patients who received higher-dose peginterferon also received a lower and fixed dose of ribavirin (800 mg/d) because of concerns about potentiating anemia. A secondary data analysis showed that the overall SVR rates were significantly related to the dose of ribavirin, and the optimal dose was identified as 13 ± 2 mg/kg. Rates of SVR were higher, at 61%, for patients receiving more than 10.6 mg/kg of ribavirin (equivalent to 800 mg/d for a 75-kg patient).

In the second major trial,⁵ 1,121 patients were randomized to 48 weeks of one of the following regimens:

- Peginterferon alfa-2a (180 µg/wk) and ribavirin (1,000 or 1,200 mg/d, based on body weight)
- Peginterferon alfa-2a (180 µg/wk) and placebo
- Nonpegylated interferon alfa-2b (3 million units three times weekly) and ribavirin (1,000 or 1,200 mg/d, based on body weight).

The overall SVR rates were 56% with peginterferon and ribavirin, 45% with nonpegylated interferon alfa and ribavirin, and 30% with peginterferon monotherapy. Among patients receiving peginterferon and ribavirin combination therapy, SVR rates were 46% for patients with HCV genotype 1 compared with 76% for patients with genotypes 2 or 3. Pretreatment factors associated with SVR in this trial included an HCV genotype other than genotype 1, age less than 40 years, and weight below 75 kg.

These two studies demonstrated that the use of peginterferon in combination with ribavirin resulted

in higher SVR rates compared with nonpegylated interferon alfa and ribavirin. As a result, the FDA has approved the use of both peginterferons in combination with ribavirin for previously untreated patients with chronic hepatitis C. The regimens approved for use in the United States are:

- Peginterferon alfa-2b 1.5 µg/kg/wk and ribavirin 800 mg/d
- Peginterferon alfa-2a 180 µg/wk and ribavirin 1,000 mg/d (for patients with body weight < 75 kg) or 1,200 mg/d (for those with body weight ≥ 75 kg).

However, patients in these two trials were treated for 48 weeks, and the optimal treatment duration based on genotype or other favorable characteristics could not be clearly defined. The optimal dose of ribavirin for use in combination with peginterferon alfa-2b has not been clearly delineated, and in the European Union a higher standard dose (800 to 1,200 mg/d, based on body weight) has been approved. Large-scale trials of weight-based dosing of ribavirin with peginterferon alfa-2b are under way in the United States.

The third major trial⁶ evaluated a shorter duration of therapy with peginterferon alfa-2a and ribavirin. A total of 1,284 patients with chronic hepatitis C were initially stratified by HCV genotype and viral load and were then randomized to receive peginterferon alfa-2a (180 µg/wk) and ribavirin (800 mg/d or higher weight-based doses [1,000 or 1,200 mg/d]) for 24 or 48 weeks. Among patients with genotype 1, 24 or 48 weeks of therapy with the higher doses of ribavirin yielded SVR rates of 41% and 51%, respectively. Among patients with other genotypes, SVR rates ranged from 73% to 78% irrespective of the duration of therapy (24 or 48 weeks) or the ribavirin dose.

These prospective results⁶ confirm prior reports and indicate that patients with genotypes 2 or 3 can be treated with 24 weeks of peginterferon and a lower dose of ribavirin (800 mg/d) with excellent virologic response rates. They also confirm that patients with genotype 1 need to receive 48 weeks of peginterferon therapy with higher doses of ribavirin. This study supports the previous study⁴ that suggested that 800 mg/d of ribavirin is suboptimal, particularly in patients with genotype 1 and higher HCV RNA levels.

■ COMPARING THE PEGYLATED INTERFERONS

Differences in the molecular weights of the PEG moieties attached to peginterferon alfa-2a and peginterferon alfa-2b result in different pharmacokinetic profiles. However, there have been no head-to-head

comparisons of the two peginterferons in clinical trials. Post hoc analytic comparisons between the published trials are confounded by variations in the patient population (such as differences in weight, genotype, viral load, and the proportion of patients with significant fibrosis), the criteria governing dose reduction and discontinuation, the assays used for HCV RNA determination, and the dosing of ribavirin, which was suboptimal in one of these studies.

Still, both compounds allow for more convenient once-weekly dosing and, when combined with ribavirin for 48 weeks, appear to result in overall SVR rates of 54% to 56%, which represents an incremental benefit over the previously accepted combination of nonpegylated interferon alfa and ribavirin. A study is now under way to compare the safety, efficacy, and side-effect profiles of the two approved peginterferon and ribavirin regimens in nearly 3,000 patients with HCV genotype 1.

■ AN EARLY PREDICTOR OF RESPONSE: HCV RNA LEVEL AT 12 WEEKS

Although several pretreatment host or viral factors (such as HCV genotype 2 or 3, lower viral burden, minimal or no fibrosis) are associated with a higher likelihood of SVR, these factors cannot accurately identify individual patients who will respond to therapy. Ideal predictors of response should identify patients who are least likely to respond, thus avoiding the side effects and expense of continued therapy.

One useful marker of outcome following initial treatment with peginterferon and ribavirin is the presence or absence of an early virologic response (EVR), defined as a decline in HCV RNA of at least 2 log₁₀ units (ie, a 100-fold decrease) or to undetectable levels by the first 12 weeks of treatment. A patient who does not achieve an EVR has a minimal (1.6%) chance of achieving SVR with continued treatment.⁷ Thus, patients with HCV genotype 1 should have their serum HCV RNA measured at week 12 of therapy, and those who do not achieve EVR should discontinue therapy. Patients with genotypes 2 or 3 have excellent SVR rates with 24 weeks of therapy with peginterferon and ribavirin, and they do not need an assessment of their HCV RNA levels at week 12.

Although they are useful in guiding treatment decisions during initial therapy for patients with HCV genotype 1, early-stopping rules based on viral burden or kinetics do not take into account assay precision or the intrinsic variability in HCV RNA levels.

Likewise, potential histologic benefits of combination therapy in virologic nonresponders may be overlooked if therapy is stopped early.

ADHERENCE TO THERAPY IS KEY TO RESPONSE

Adherence to therapy enhances the likelihood of achieving virologic response. A retrospective analysis of the trials comparing combination therapy with either nonpegylated interferon alfa-2b or peginterferon alfa-2b plus ribavirin showed that patients receiving at least 80% of both drugs for at least 80% of the expected duration of therapy had enhanced SVR rates compared with the intent-to-treat analysis for the overall patient population in these studies.⁸ Among patients who received peginterferon alfa-2b (1.5 µg/kg/wk) and ribavirin (800 mg/d), the SVR rate rose from 54% for the overall treatment group to 63% for adherent patients (as adherence was defined above); this increase resulted from an adherence-related improvement in SVR rates from 42% to 51% among patients with HCV genotype 1. Patients with genotype 2 or 3 already had excellent SVR rates, so 80% adherence to therapy did not appear to significantly enhance SVR in this group.

There also appeared to be a direct relation between different levels of adherence and SVR in this analysis.⁸ For example, a level of 20% adherence reduced overall SVR rates to only 16% to 17%. Although this analysis also assessed the impact of early versus late adherence, most patients who had dose reduction early in therapy also maintained this lower dose throughout the study period. The number of patients who were nonadherent in the initial 12 weeks and became adherent thereafter was too small to allow a comparative analysis.

Another study retrospectively evaluated the relation between EVR rates and adherence in patients who received peginterferon alfa-2b (1.5 µg/kg/wk) and ribavirin (800 mg/d).⁹ Reduction of the dose of either peginterferon alfa-2b or ribavirin to less than 80% of the full level was noted in 20% of patients in the first 12 weeks of therapy, and it lowered the EVR rate from 80% for patients who received full doses to 70% for those with peginterferon reductions and to 60% for those with ribavirin reductions. Dose reduction or discontinuation of both drugs resulted in a significant reduction in EVR rates, from 80% to 33%. Patients whose dose of either drug was reduced to less than 80% of the full dose following an EVR had a reduction in their chance of an eventual SVR, from 72% to 62%. Moreover, if the duration of ther-

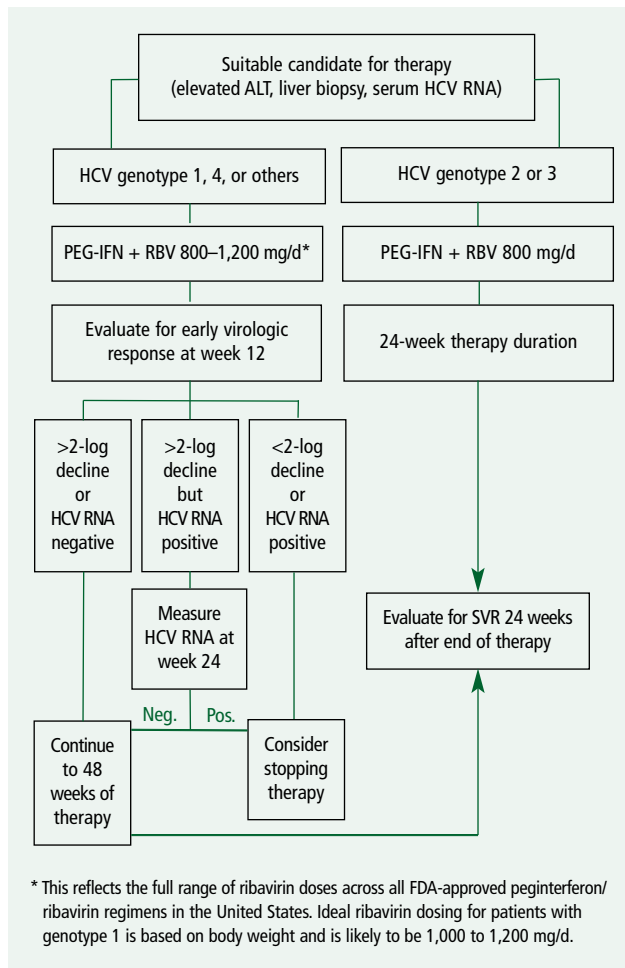


FIGURE 1. Treatment algorithm for previously untreated patients with chronic hepatitis C virus (HCV) infection (ALT = alanine aminotransferase; PEG-IFN = pegylated interferon; RBV = ribavirin; SVR = sustained virologic response).

apy was less than 80% of the expected duration, the chance of an eventual SVR in these patients was only 50%.

Thus, maintaining at least 80% adherence to the prescribed regimen of peginterferon and ribavirin in the first 12 to 24 weeks of therapy is likely to enhance virologic response rates, particularly in the difficult-to-treat patients with HCV genotype 1. A multifaceted team approach to improving adherence is certainly important, and it includes patient education about the treatment regimen, addressing social and psychological issues, managing side effects, providing advice on possible lifestyle change, referral to support groups, and frequent follow-up visits or telephone interviews, as well as providing patients with educational materials, pill boxes, self-monitoring devices, and reminders. This type of approach is discussed in

detail in the final article in this supplement, by Gujral and colleagues.

■ CONCLUSIONS, REMAINING CHALLENGES

The current standard of care in previously untreated patients with chronic hepatitis C is combination therapy with peginterferon and ribavirin. The duration of therapy and the ribavirin dose should be determined according to the patient's HCV genotype (**Figure 1**). Patients with genotype 1 should receive 48 weeks of treatment with peginterferon and ribavirin (1,000 or 1,200 mg/d, based on weight). Patients with genotype 2 or 3 can be given 24 weeks of therapy that includes a lower dose of ribavirin (800 mg/d). Until further data are available, patients with other genotypes (such as 4, 5, or 6) should be treated like patients with genotype 1. Patients who have contraindications to ribavirin may be considered for treatment with peginterferon alone for 48 weeks,

although virologic response rates are likely to be lower. The absence of an EVR is a good early predictor of nonresponse, providing guidance for whether to continue therapy in patients with genotype 1; such early-stopping rules may encourage adherence to therapy in the initial weeks of treatment.

Studies in the near future will examine optimal dosing schedules for peginterferons, the role of adjunctive therapy with growth factors or antidepressants, and strategies for increasing sustained response to current therapy. Further studies are needed to better delineate the influence on virologic response of host factors such as race, obesity, and steatosis. Despite the important gains of recent years, current therapies are suitable only for select populations with chronic hepatitis C. There remains a significant need to develop effective alternative therapies that are well-tolerated, cost-effective, and available to all patients.

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Retreatment of patients who do not respond to initial therapy for chronic hepatitis C

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■ ABSTRACT

Despite improvements in the treatment of chronic hepatitis C virus (HCV) infection, nearly half of all patients do not respond to initial therapy. Retreatment of these patients with pegylated interferon and ribavirin has been successful in only a limited percentage of cases. Factors associated with sustained virologic response (SVR) following retreatment include prior treatment with interferon monotherapy, HCV genotype 2 or 3, a low serum HCV RNA level, and the absence of cirrhosis. Fewer than 6% of nonresponders who were previously treated with interferon and ribavirin and who have cirrhosis, genotype 1, and a high viral load achieve SVR following retreatment with pegylated interferon and ribavirin. No therapy has been shown to yield SVR in patients who do not respond to pegylated interferon and ribavirin. Long-term maintenance therapy with pegylated interferon is currently being evaluated in nonresponders with advanced fibrosis and cirrhosis. Its use should be considered investigational at this time.

As each new and more effective therapy for chronic hepatitis C virus (HCV) infection has emerged, patients who were unresponsive to previous therapy and their physicians have been eager to embark on retreatment, expecting the newer therapy to be much more effective

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than the one they had used before. That's understandable, given the dramatic improvements in therapy for HCV infection detailed in the first two articles in this supplement. Unfortunately, however, only a limited number of patients who are unresponsive to initial therapy (nonresponders) will benefit from retreatment. It is therefore important to recognize the factors associated with continued nonresponse so that these patients may avoid the side effects, costs, and continued frustration associated with ineffective therapy. This article reviews emerging data on the efficacy of retreatment in patients with chronic HCV infection who have not responded during previous therapy.

■ RETREATMENT OPTIONS

The goal of retreatment is to achieve sustained virologic response (SVR), defined as the absence of serum HCV RNA 24 weeks after the end of therapy. However, this cannot be accomplished unless the patient first responds and achieves undetectable serum HCV RNA levels during retreatment. For this to happen, the patient needs to be retreated with a more effective therapy than he or she received previously. Since the most effective therapy currently available for chronic HCV infection is the combination of pegylated interferon alfa (peginterferon) and ribavirin, all nonresponders should be retreated with this regimen.

Retreatment with peginterferon and ribavirin

The HALT-C (Hepatitis C Antiviral Long-term Treatment against Cirrhosis) trial¹ is the first and largest study to date to evaluate the efficacy of retreatment with peginterferon and ribavirin in nonresponders to prior interferon-based therapy. Results from the first 604 patients in this ongoing trial demonstrate that SVR was achieved in 18% of patients overall, including:

- 11% of patients previously treated with interferon and ribavirin
- 14% of patients with HCV genotype 1
- 15% of patients with a serum HCV RNA level

TABLE 1

Factors to assess when considering retreatment in a patient with hepatitis C virus (HCV) infection

Fixed factors

- Race
- HCV genotype
- Serum HCV RNA level
- Previous therapy and the response to it
- Severity of liver disease

Correctable factors

- Use of therapy with suboptimal effectiveness
- Overaggressive dose reduction
- Nonadherence to recommended therapy
- Severe anemia requiring dose reduction within first 12 weeks of therapy
- Ongoing alcohol or illicit drug use
- Lack of patient or physician commitment to therapy

greater than 1.5×10^6 IU/mL

- 11% of patients with cirrhosis.

Moreover, patients with all four of these factors had an SVR rate of only 6%. African Americans responded poorly to retreatment, with SVR observed in only 6%.

As in the treatment-naïve population, failure to achieve early virologic response (EVR) remains an excellent predictor of continued nonresponse. In the HALT-C trial,¹ only 1% of nonresponders who did not achieve an EVR after 12 weeks of retreatment with peginterferon and ribavirin went on to SVR.

Patients who do not achieve EVR or in whom serum HCV RNA levels are still detectable within 24 weeks of treatment (or retreatment) with peginterferon and ribavirin will not achieve virologic response with ongoing therapy. Treatment should be discontinued in these patients as soon as nonresponse is recognized. The possible role for continuing peginterferon as maintenance therapy, to prevent histologic progression in nonresponders, will be discussed below.

Retreatment with consensus interferon

Consensus interferon is a synthetic interferon product with an amino acid sequence that reflects all alpha interferons. Prior to the use of ribavirin as combination therapy, consensus interferon monotherapy was shown to be effective for retreatment of nonresponders to monotherapy with nonpegylated interferon, achieving an SVR in 13% of these previous nonresponders.² However, no SVR data are available regarding retreatment with consensus interferon and ribavirin in patients previously unresponsive to either

nonpegylated interferon and ribavirin, peginterferon monotherapy, or peginterferon and ribavirin.

Investigational therapies for retreatment

Several agents are currently being evaluated in clinical trials for use in nonresponders.

Amantadine is an antiviral agent used to treat influenza A. For the treatment of chronic HCV infection, amantadine has been used alone, in combination with interferon, or as triple therapy with interferon and ribavirin. A meta-analysis has suggested that SVR rates may be about 5% to 7% higher in patients treated with amantadine, interferon, and ribavirin compared with patients receiving interferon and ribavirin alone.³ Whether amantadine would improve SVR rates during retreatment with peginterferon and ribavirin remains unexplored and speculative.

Thymosin alpha-1 is a synthetic peptide derivative of a purified thymus gland extract that modulates several pathways in the immune response to various viruses. A single study⁴ has shown that the combination of interferon and thymosin alpha-1 may increase SVR rates compared with interferon alone. Ongoing studies are evaluating the efficacy of combination therapy with peginterferon and thymosin alpha-1 in nonresponders.

ISIS 14803 is a 20-base antisense phosphorothioate oligodeoxynucleotide to the highly conserved IRES/translation initiation region of HCV. It is administered via intravenous infusion or subcutaneous injection. In preliminary studies, a 1-log to 2-log reduction in serum HCV RNA was observed when ISIS 14803 was given to nonresponders to interferon.⁵ Use of this agent in combination with peginterferon is currently being explored as a treatment for nonresponders.

ASSESSING FACTORS BEFORE RETREATMENT

A number of factors should be considered before attempting to retreat a patient who did not achieve SVR during a previous course of interferon-based therapy. These factors can be divided into two broad categories: fixed and correctable. Fixed factors, outlined in **Table 1**, are those that cannot be altered or corrected before initiating retreatment. A demographic factor such as race is a very important fixed factor to consider, since African American patients respond poorly to retreatment. Correctable factors, also listed in **Table 1**, are those that can be modified; if correctable factors are modified, the patient may respond to retreatment.

Fixed factors

As noted above, HCV genotype 1, a high viral load, cirrhosis, and previous treatment with interferon and

ribavirin are associated with a low likelihood of responding to retreatment with peginterferon and ribavirin. In the HALT-C trial,¹ only 6% of patients with all four of these fixed factors for a poor prognosis achieved SVR following retreatment. Therefore, the reason for offering retreatment in this setting must be compelling.

In contrast, fixed factors associated with an excellent response to retreatment include HCV genotypes 2 or 3, a serum HCV RNA level less than 1.5×10^6 IU/mL, and prior treatment with only interferon monotherapy. Patients with these characteristics have SVR rates of 25% to 65% following retreatment with peginterferon and ribavirin.¹ Retreatment of patients with favorable fixed factors (Table 2) should therefore be strongly considered.

Partial virologic response. An often overlooked but important group of nonresponders to consider for retreatment are patients with a *partial virologic response*, ie, an excellent decline in serum HCV RNA during treatment that nonetheless falls short of viral undetectability. In a study in which nonresponders to interferon monotherapy were retreated with interferon and ribavirin, SVR was achieved only in those patients who had a partial virologic response during the previous therapy.⁶ Partial virologic response in that study was defined as a decline in serum HCV RNA to less than 100,000 copies/mL.

Retreatment of patients with partial virologic response is particularly likely to be successful if the suboptimal response was the result of a reduction in the dose or premature discontinuation of interferon or ribavirin, and if this dose reduction can be prevented during retreatment.

Correctable factors

Ongoing alcohol or illicit drug use. Ongoing heavy alcohol consumption appears to impair the antiviral effects of interferon and reduce the chance of SVR.⁷ Response to therapy also appears to be reduced in patients with ongoing illicit drug use, and this appears to be related primarily to a high rate of psychiatric side effects and nonadherence. Nonresponders who consumed alcohol or used illicit drugs on a regular basis during previous therapy may therefore be good candidates for retreatment, but only if they have demonstrated long-term abstinence and are committed to remaining abstinent.

Lack of commitment to prior therapy. Many patients who begin interferon-based therapy for chronic HCV infection are not aware of the side effects of treatment, are nonadherent to the prescribed regimen because of personal or work-related activities, or sim-

TABLE 2
Factors associated with a favorable response during retreatment of hepatitis C virus (HCV) infection

- Prior treatment with interferon alone
- Non-African race
- HCV genotype 2 or 3
- Low serum HCV RNA level
- Absence of cirrhosis

ply do not receive proper counseling about side-effect management from their physician. A preliminary report⁸ has suggested that SVR rates may be up to 20% higher when patients are treated by physicians who are highly experienced in prescribing and managing the side effects of interferon therapy. Improved awareness of these side effects and a stronger commitment to therapy on the part of some patients may yield higher rates of SVR during retreatment, as may the transfer of selected patients' care to a more experienced or attentive interferon prescriber.

Dose reduction. Reducing the dose of ribavirin, especially during the first 12 to 24 weeks of treatment, impairs the ability of patients with HCV genotype 1 to achieve SVR. The first study to report this observation⁹ noted that when the dose of either interferon (pegylated or nonpegylated) or ribavirin was reduced by more than 20% from the originally prescribed level, SVR rates declined from 51% to 34%. In contrast, patients in whom the dose of either of these medications was reduced after week 12 had a smaller decline in SVR rates—from 62% to 51%. Additional data suggest that reducing the dose of ribavirin, but not interferon, within the first 12 to 20 weeks of treatment reduces the likelihood of both EVR and SVR.^{1,10} In contrast, reducing the dose of ribavirin after HCV RNA levels already have become undetectable appears to have little effect on SVR rates.

Recent studies^{11,12} have suggested that erythropoietic growth factors such as epoetin alfa may prevent interferon- and ribavirin-induced anemia and thereby prevent the need to reduce the dose of ribavirin. However, these studies have not demonstrated that SVR rates are increased when epoetin alfa is used. When the lack of response to previous therapy may have resulted from ribavirin dose reduction during the first 12 weeks of therapy, using epoetin alfa during retreatment may enable select patients to achieve SVR. In contrast, the current data do not suggest that

using growth factors to enhance neutrophil or platelet counts, in lieu of reducing the dose of peginterferon, will reduce rates of nonresponse.

■ LIVER HISTOLOGY LOOMS LARGE IN RETREATMENT DECISIONS

The availability a new therapy, either established or experimental, for use in retreatment does not imply that a nonresponder must be retreated, nor does the identification of a potentially correctable factor. The decision to retreat should be well thought out and should balance the need for retreatment with the likelihood that the new treatment will be successful. Such a decision cannot be made without knowing the severity of the patient's liver disease and without estimating the patient's risk of developing cirrhosis in the near future. As a result, it is important that an assessment of liver histology be performed before deciding if retreatment is appropriate. Patients whose risk factors and presumed infection with HCV date back 20 years or more and who have no fibrosis or minimal fibrosis on liver biopsy have an excellent prognosis. Fewer than 25% of such patients will develop cirrhosis over the next 10 years.¹³ Because retreatment is unlikely to be successful in the setting of several fixed factors that suggest continued nonresponse, simply monitoring nonresponders who have no fibrosis or mild fibrosis is probably a more rational option.

■ A ROLE FOR MAINTENANCE THERAPY IN NONRESPONDERS WITH CIRRHOSIS?

It is well established that patients who achieve SVR have an improvement in liver histology scores.¹⁴⁻¹⁷ At the same time, it appears that some nonresponders also achieve such benefit. This is most likely to occur in nonresponders who have a marked reduction in serum HCV RNA during therapy. Continuing interferon (as monotherapy) in such patients was shown to maintain the histologic improvement.¹⁸ In contrast, discontinuing interferon therapy in a nonresponder with histologic improvement is associated with regression of liver histology back to the pretreatment baseline within 1 to 2 years.¹⁸

Several clinical trials are currently evaluating the benefits of maintenance peginterferon therapy in patients with advanced bridging fibrosis or cirrhosis. The goal of these trials is to determine whether continuing peginterferon therapy over several years can prevent fibrosis progression and hepatic decompensation. The HALT-C trial¹ is the largest and most publicized of these studies. Results from this and similar trials will not be available for several years. Until then,

the use of peginterferon maintenance therapy to prevent fibrosis progression in nonresponders should be considered unproven. However, maintenance therapy might be beneficial in select nonresponders with cirrhosis who had a marked decline in serum HCV RNA during therapy. How much of a decline in serum HCV RNA level is sufficient remains to be defined.

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Managing the hematologic side effects of antiviral therapy for chronic hepatitis C: Anemia, neutropenia, and thrombocytopenia

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■ ABSTRACT

Hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia are common during combination therapy with pegylated (or standard) interferon and ribavirin for chronic hepatitis C. Ribavirin-induced hemolytic anemia is a common cause of dose reduction or discontinuation. Bone marrow suppression also contributes to the anemia and is the predominant mechanism for interferon-induced neutropenia and thrombocytopenia. Although dose reduction or discontinuation of combination therapy can reverse these abnormalities, they may reduce virologic response. Hematopoietic growth factors may provide a useful alternative for managing these hematologic side effects without reducing the optimal dose of the combination antiviral regimen. Treatment of anemia also may improve patients' health-related quality of life and their adherence to combination antiviral therapy. The impact of growth factors on sustained virologic response and their cost-effectiveness in patients with chronic hepatitis C need further assessment.

The most effective therapeutic regimen for infection with hepatitis C virus (HCV) today is the combination of pegylated interferon alfa and ribavirin (combination therapy),

which yields sustained virologic response (SVR) in up to 56% of patients.^{1,2} However, one of the main drawbacks of this combination therapy (and also of regimens combining nonpegylated interferon with ribavirin) is the development of side effects, which can result in suboptimal dosing or discontinuation of therapy. That can limit the likelihood of SVR, since one of the determinants of SVR is adequate dose and duration of therapy, as previously discussed in this supplement. Among the side effects of combination therapy, hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia have been reported to result in dose reduction and discontinuation of therapy in up to 25% and 3% of patients, respectively.³

Management of hematologic abnormalities during antiviral therapy for HCV infection can be an important strategy for maximizing treatment outcomes. While information on the use of hematopoietic growth factors during therapy for HCV infection remains preliminary, these agents are important since they can be helpful as adjuncts to antiviral therapy. This review explores the incidence, clinical significance, and management of anemia, neutropenia, and thrombocytopenia associated with combination therapy for HCV infection.

■ ANEMIA

A leading cause of dose reduction and discontinuation

Among the hematologic abnormalities associated with combination therapy, anemia is probably the most significant, as it can reduce patients' health-related quality of life and may be the main determinant of fatigue.⁴ A pooled analysis of data from three large trials comparing pegylated interferon (peginterferon) with nonpegylated interferon determined that worsening of fatigue scores was a significant predictor of treatment discontinuation.⁵ Interruption and premature discontinuation of antiviral therapy decreases the efficacy of antiviral therapy. In large multicenter clinical trials of

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combination therapy for HCV infection, dose reduction for anemia occurred in up to 23% of patients.^{1,2} Discontinuation was uncommon in these trials, but the rate of discontinuation is higher outside of clinical trials. In one study that evaluated “real world” patients, anemia was the leading cause of premature discontinuation of combination therapy, accounting for 36% of all discontinuations (ie, in 8.8% of all patients).⁶

Significant anemia (ie, hemoglobin < 10 g/dL) has been observed in up to 9% to 13% of patients receiving combination therapy with interferon and ribavirin.¹ Moderate anemia (hemoglobin < 11 g/dL) may be seen in 30%.⁷ The mean maximal decrease in hemoglobin can be as high as 3.1 g/dL and 3.7 g/dL with nonpegylated and pegylated interferon, respectively, in combination with ribavirin.^{2,8} The hemoglobin generally reaches its lowest level within the first 4 to 8 weeks of therapy, plateauing thereafter and returning to baseline values after treatment discontinuation.

Both ribavirin and the interferons contribute

There are several mechanisms by which anemia occurs during combination therapy for HCV infection. Ribavirin causes a dose-dependent and reversible hemolytic anemia. After entering red blood cells, ribavirin is phosphorylated into its active form, leading to depletion of adenosine triphosphate.⁹ This leads to impaired antioxidant mechanisms, resulting in membrane oxidative damage and subsequent extravascular red blood cell removal by the reticuloendothelial system.⁹

Interferons also contribute to anemia, mainly through bone marrow suppression.¹⁰ De Franceschi and colleagues⁹ found that interferon impairs compensatory reticulocytosis related to ribavirin-induced hemolytic anemia, suggesting that the bone marrow-suppressive effect of interferon contributes to the anemia associated with combination therapy.

Managing by dose reduction—and the limits thereof

There are widely variable approaches to the management of anemia during combination therapy. The package insert for ribavirin recommends reducing the ribavirin dose at hemoglobin levels less than 10 g/dL and permanently discontinuing the drug at levels less than 8.5 g/dL. As previously noted (see the article by Patel and McHutchison in this supplement), such dose reduction can have adverse implications for SVR, since studies show that higher doses of ribavirin are associated with higher SVR rates. Rates of SVR are higher in patients who receive more than 80% of their full interferon and ribavirin doses for more than 80% of the intended duration of therapy.¹¹ One report

found that SVR rates were higher in patients who received greater than 10.6 mg/kg/d of ribavirin.¹ In fact, delivering the optimal dose of antiviral therapy seems to be most crucial during the first 12 weeks of antiviral therapy, the period of most significant decline in hemoglobin.¹²

A role for erythropoietic growth factors?

An alternative strategy for raising hemoglobin levels without resorting to dose reduction or premature withdrawal is the use of erythropoietic growth factors.

Epoetin alfa. Recombinant human erythropoietin, commercially available as epoetin alfa, is used to treat anemia associated with chronic renal failure, zidovudine therapy for HIV infection, or cancer chemotherapy, as well as to reduce the need for blood transfusions in anemic patients undergoing elective surgery.

Two studies have evaluated the use of epoetin alfa as an adjunct for the management of anemia (defined as hemoglobin < 12 g/dL) during combination therapy for chronic hepatitis C. Dieterich and colleagues¹³ compared epoetin alfa therapy (40,000 units weekly) with standard-of-care anemia management in 64 patients in terms of the effects on hemoglobin levels and ribavirin dose. They found that patients receiving epoetin alfa had increases in hemoglobin level and maintained their ribavirin dose. At 16 weeks after randomization, the patients who received epoetin alfa had significantly higher mean hemoglobin levels (14.2 vs 11.2 g/dL) and a higher mean ribavirin dose (895 vs 707 mg/d) compared with the patients who received standard anemia management. Also, significantly fewer patients in the epoetin alfa group had their ribavirin dose reduced (5.7% vs 33.3%), and significantly more patients in the epoetin alfa group maintained a daily ribavirin dose of 800 mg or greater (83% vs 54%).

In the other study,¹⁴ 186 patients from several centers were randomized to receive epoetin alfa (40,000 to 60,000 units weekly) or placebo. After 8 weeks, patients receiving epoetin alfa showed improvement in their anemia and were more likely than placebo recipients to maintain their ribavirin dose from randomization. These patients also had higher mean hemoglobin levels and higher mean ribavirin doses than the placebo recipients. This study had an open-label period during which patients receiving epoetin alfa who were responding to this treatment continued their medication and those receiving placebo who developed anemia and/or required ribavirin dose reduction were started on epoetin alfa. During follow-up in the open-label period, no further changes were

noted in patients previously taking epoetin alfa, whereas patients who previously had taken placebo showed significant increases in hemoglobin levels. The investigators also found that improvement in hemoglobin was an independent predictor of improvement in health-related quality of life as measured by the Linear Analog Scale Assessment and the Medical Outcomes Survey Short Form-36.¹⁵ They suggested that since epoetin alfa increases hemoglobin levels in anemic HCV-infected patients receiving combination therapy, it may also improve health-related quality of life in these patients.

Neither of these two studies was designed to evaluate the effect of epoetin alfa on virologic response. Epoetin alfa was generally well tolerated in both studies.

Darbepoetin alfa. Darbepoetin alfa is a novel erythropoietic protein recently approved by the US Food and Drug Administration for treatment of anemia associated with chronic renal failure and cancer chemotherapy. Darbepoetin alfa is a hyperglycosylated protein, which gives it a threefold longer circulating half-life, higher in vivo potency, and less-frequent dosing compared with epoetin alfa.¹⁶ Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. In a number of clinical trials of patients receiving cancer chemotherapy, darbepoetin alfa had the same efficacy and safety profile as epoetin alfa but required less-frequent dosing.¹⁶

Preliminary data from a recent study¹⁷ show that darbepoetin alfa therapy (3 µg/kg every other week) in patients with chronic hepatitis C increases hemoglobin levels and also allows for maintenance of the optimal weight-based dose of ribavirin in 83% of patients, suggesting that it may be beneficial as an adjunct to combination therapy for HCV infection. Improvements in health-related quality of life also were noted after initiation of darbepoetin alfa. To date, no significant toxicity has been noted with the use of darbepoetin alfa in this study.

Darbepoetin alfa's increased half-life and less-frequent dosing may simplify anemia management, potentially offering greater convenience to both patients and health care providers.

Additional issues to address. These studies are promising and should provide impetus for larger trials that can adequately address issues such as the optimal dose and duration of erythropoietic growth factor therapy, the effect of improvement in anemia on SVR, quality of life, treatment adherence, efficiency of care delivery, and cost-effectiveness. The hemoglobin level that should trigger the initiation of growth

factor therapy and the target hemoglobin level to be achieved are other important issues to consider.

■ NEUTROPENIA

Interferon therapy is associated with a reduction in peripheral white blood cell counts (both neutrophils and lymphocytes). This has been attributed to bone marrow suppression or a reversible impairment in the release of neutrophils and lymphocytes.¹⁰ Peginterferons result in a greater degree of neutropenia than does nonpegylated interferon. Similar to hemoglobin levels, neutrophil counts decline rapidly within the first 2 weeks of therapy, stabilize for the duration of therapy, and rapidly return to baseline levels after treatment discontinuation.

Reducing the interferon dose is a common strategy

Because of concerns about the association between neutropenia and infections, the package inserts of both peginterferon preparations (alfa-2a and alfa-2b) recommend dose reduction for patients with neutrophil counts less than 750 cells/mm³ and drug discontinuation for those with counts less than 500 cells/mm³. In the pivotal trials of combination therapy with peginterferon and ribavirin, neutropenia was the most frequent reason for reducing the peginterferon dose.^{1,2} Neutropenia-related dose reductions took place in 24% and 18% of patients receiving peginterferon alfa-2a and alfa-2b, respectively. Less than 1% of patients required permanent drug discontinuation.

Although reducing the dose of peginterferon can, like ribavirin dose reduction, also reduce the likelihood of SVR, this impact has been less clearly established. In the large multicenter study of peginterferon alfa-2b and ribavirin,¹ patients who were randomized to peginterferon 1.5 mg/kg/wk for 1 month followed by 0.5 mg/kg/wk had significantly lower SVR rates than did those who received 1.5 mg/kg/wk for the duration of therapy. This suggests that maintenance of the optimal dose of peginterferon for the entire duration of treatment may also be a determinant of long-term virologic response.

The neutrophil count threshold used for dose modification was extrapolated from data in cancer patients who developed neutropenia related to chemotherapy. The implications of these data for interferon-related neutropenia in patients with hepatitis C are not wholly clear. In a systematic analysis of bacterial infections in 119 patients receiving interferon and ribavirin, none of the 22 infections that occurred during treatment were observed in neutropenic patients.¹⁸ The only bacterial infection that required hospital admission was in a patient with cirrhosis who had a neutrophil count

greater than 1,000 cells/mm³. These findings suggest that neutropenia may be better tolerated by HCV-infected patients receiving combination therapy than it is by cancer patients receiving chemotherapy.

Management looks to granulocyte colony-stimulating factor

The management of neutropenia, like that of anemia, is variable. While some clinicians tolerate more profound neutropenia before recommending dose reduction, others are using filgrastim to raise the neutrophil count in HCV-infected patients receiving combination therapy.

Filgrastim is a recombinant human granulocyte colony-stimulating factor (G-CSF) that is used to increase white blood cell and neutrophil counts in cancer patients with chemotherapy-associated neutropenia. Very few studies have reported the use of filgrastim in patients with chronic hepatitis C. Van Thiel and colleagues¹⁹ evaluated filgrastim as an adjunct to interferon in HCV-infected patients with advanced liver disease. All 30 patients had histologically confirmed cirrhosis. They were randomly assigned to receive interferon alfa-2b alone or with 300 mg of filgrastim given twice a week. The dose of interferon alfa-2b was 5 MU daily. Although the mean and peak white blood cell counts were higher for the patients receiving filgrastim, the nadir values were the same between the two treatment groups. A higher proportion of patients receiving filgrastim (53% vs 40%) achieved SVR, but this difference was not statistically significant. Filgrastim appeared to be fairly well tolerated in this study.

In a more recent study,²⁰ the use of filgrastim allowed patients to resume and maintain their full dose of peginterferon. In an additional study,¹⁷ filgrastim was used to manage neutropenia in 39 patients who were treated with peginterferon alfa-2b and ribavirin. Preliminary results from this study demonstrate that 89% of patients receiving filgrastim had significant improvement in their neutrophil count (Younossi, unpublished data, 2004).

Together, these results indicate that filgrastim may be safe and effective in raising neutrophil counts in HCV-infected patients undergoing antiviral therapy. Nevertheless, future research will be important to better understand the clinical implications and management of neutropenia in these patients.

■ THROMBOCYTOPENIA

A decrease in platelet count also may be observed in patients who are receiving interferons, and such decreases are more prominent with the peginterfer-

ons. The decrease is caused primarily by a reversible bone marrow suppression, although autoimmune-related thrombocytopenia may also occur. The concurrent use of ribavirin may blunt the thrombocytopenic effect of interferons as a result of reactive thrombocytosis.

With peginterferons, the platelet count decreases gradually over 8 weeks, stabilizing thereafter and returning to baseline values within 4 weeks of stopping therapy. Bleeding complications as a result of thrombocytopenia are uncommon.^{1,2}

In randomized clinical trials of the peginterferons, the rate of dose reduction attributed to thrombocytopenia ranged from 3% to 6%.^{1,2} However, most patients in clinical trials are carefully selected, and these trials excluded patients with more advanced liver disease. Patients with cirrhosis may have baseline thrombocytopenia due to hypersplenism from portal hypertension, and these patients may develop more significant decreases in platelet counts owing to bone marrow suppression during therapy. For these patients, an alternative approach to dose modification would be beneficial to avoid dose reduction or discontinuation, both of which reduce the chance of SVR.

Early, unencouraging results with interleukin-11

Data are even more limited on the use of growth factors for the management of interferon-related thrombocytopenia than for the management of interferon-related anemia and neutropenia. Oprelvekin, or recombinant human interleukin-11, is approved for use in cancer patients receiving chemotherapy to enhance platelet production. It also may be useful as adjuvant therapy in HCV-infected patients receiving combination therapy.

Oprelvekin was evaluated in an open-label study of 13 HCV-infected patients undergoing therapy with interferon (3 MU three times per week) and ribavirin (1,000 to 1,200 mg/d) for 48 weeks.²¹ All patients had low baseline platelet counts (< 100,000 cells/mm³). Oprelvekin was given concurrently at a dose of 50 mg/kg subcutaneously three times per week. The researchers noted improvement in platelet counts: the mean count at 2 weeks was higher than the baseline count (98,600 vs 73,600 cells/mm³; *P* < .05). The main side effect was fluid retention, which was noted in all patients, with 10 of 13 patients requiring diuretic therapy.

Given this side-effect profile in patients with HCV-related cirrhosis, there currently is not much enthusiasm for oprelvekin's use. Newer growth factors

with more promising safety and efficacy profiles are in development.

■ CONCLUSIONS

Hematologic abnormalities are common during combination antiviral therapy for chronic hepatitis C. Although dose reduction or discontinuation can easily treat these side effects, they can adversely affect the efficacy of combination antiviral therapy. This is especially true in the management of ribavirin-

induced anemia. Recent evidence has led to increasing recognition that optimal dosing of ribavirin is a crucial determinant of viral clearance. Preliminary data suggest that hematopoietic growth factors may be useful for managing the hematologic side effects of combination therapy (especially anemia). The current data are limited and further study will be required, particularly with respect to the potential impact on SVR, cost-effectiveness, health-related quality of life, and other patient-related outcomes.

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The role of hematopoietic growth factors in special populations with chronic hepatitis C: Patients with HIV coinfection, end-stage renal disease, or liver transplantation

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■ ABSTRACT

Certain populations with chronic hepatitis C face special challenges in attaining optimal adherence to antiviral therapy, including patients coinfecting with human immunodeficiency virus, patients undergoing dialysis for end-stage renal disease, and liver transplant recipients. These patient groups may stand to gain particular benefit from the expanding use of hematopoietic growth factors to manage the cytopenic effects of antiviral therapy for hepatitis C. This article reviews the rationale, current evidence, and future prospects for the adjunctive use of growth factors in these special populations with hepatitis C.

The challenge of optimizing adherence to therapy for chronic hepatitis C is particularly pronounced in certain patient populations, including patients coinfecting with both human immunodeficiency virus (HIV) and hepatitis C virus (HCV), patients undergoing dialysis for end-stage renal disease (ESRD), and liver transplant recipients. The challenge stems from these populations' heightened risk of adverse effects from therapy, including enhanced susceptibility to hematologic toxicities, since these adverse effects often lead to

dose reductions or premature discontinuation of pegylated interferon alfa (peginterferon) and ribavirin, the current standard of treatment for chronic hepatitis C.

Managing chronic hepatitis C in these groups is made even more difficult by these patients' apparent risk of more rapidly progressive HCV-associated liver disease, which, in the case of patients with ESRD, pertains especially to the period following renal transplantation. Moreover, for at least two of these populations, patients with HIV/HCV coinfection and liver transplant recipients, ample evidence demonstrates impaired response to combination therapy with peginterferon and ribavirin. For patients with ESRD, ribavirin is considered contraindicated because of the risk of severe anemia.

As clinicians attempt to optimize adherence and avoid dose reductions or premature discontinuation of therapy, the use of hematopoietic growth factors has become increasingly widespread for patients with chronic hepatitis C. Consideration of these growth factors is especially warranted in the patient populations mentioned above, in light of the special challenges they face.

■ OVERVIEW OF THERAPY-INDUCED CYTOPENIAS

In the preceding article in this supplement, Ong and Younossi review in detail the hematologic side effects of combination therapy for chronic hepatitis C. Briefly, both the conventional and pegylated forms of interferon suppress hematopoiesis, often resulting in neutropenia, thrombocytopenia, and a mild reduction in hemoglobin. Ribavirin results in a dose-dependent, reversible hemolytic anemia in a significant number of patients, and when it is used in combination with interferon, the anemia is far more pronounced than with interferon alone. All of these cytopenias can be managed with dose reductions or discontinuation of peginterferon or ribavirin, but abundant data suggest that dose reductions decrease the likelihood of response to therapy.

Much interest has focused on the clinical signifi-

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cance of cytopenias induced by therapy for hepatitis C. There is no doubt that reductions in hemoglobin may result in impaired functional capacity, reduced quality of life, and even organ manifestations such as cardiac ischemia. In contrast, many clinicians have come to question the degree to which interferon-induced reductions in neutrophil count truly predispose to infection^{1,2} or to which interferon-induced thrombocytopenia predisposes to bleeding. Consequently, clinicians generally feel that the risk of clinically significant thrombocytopenia is very low and that reduced platelet counts are the least common hematologic indication for dose reduction or discontinuation. Nevertheless, all clinicians agree on the need to monitor cell counts during therapy and to react to cytopenias of sufficient severity.

■ HEMATOPOIETIC GROWTH FACTORS: RATIONALE FOR THEIR USE IN SPECIAL POPULATIONS

Recombinant erythropoietin and recombinant granulocyte colony-stimulating factor (G-CSF) have garnered interest as potential tools for limiting hematologic side effects—*anemia and neutropenia, respectively*—in patients with chronic hepatitis C who are treated with peginterferon and ribavirin. Recombinant erythropoietin has been used successfully in the management of anemia associated with chemotherapy, chronic renal failure, zidovudine therapy for HIV infection, and surgery.³ G-CSF has been used principally in the management of neutropenia associated with chemotherapy.⁴

Increasing evidence suggests that recombinant erythropoietin⁵⁻⁹ and G-CSF⁹⁻¹² may be used safely in patients treated with peginterferon and ribavirin and may potentially minimize the need for dose reductions or discontinuation of therapy, as well as improve adherence to therapy and quality of life. This may be of greatest importance in patients who face the prospect of rapidly progressive liver fibrosis and in whom hematologic side effects are common, including patients with HIV/HCV coinfection, patients with ESRD undergoing dialysis, and liver transplant recipients. However, the use of hematopoietic growth factors has not been adequately evaluated in these patients and further studies will be needed to determine the appropriate dosing and timing of therapy. Of particular note is the absence of firm data from randomized trials showing that hematopoietic growth factor use results in increased rates of sustained virologic response (SVR).

■ PATIENTS COINFECTED WITH HIV

Approximately one third of HIV-infected individuals are also infected with HCV.^{13,14} Patients coinfect

with HIV and HCV are at particular risk of developing anemia and neutropenia during therapy with peginterferon and ribavirin, as they may have underlying HIV-associated hematopoietic dysfunction.¹⁵ Although adherence analyses analogous to those from the large trials in patients infected only with HCV have not yet been presented, the need to provide an optimal course of therapy for HIV/HCV-coinfecting patients should be stressed since these patients have higher serum HCV RNA levels, accelerated fibrosis, a higher prevalence of cirrhosis, higher mortality, and lower rates of virologic response to therapy compared with patients infected with HCV alone.¹⁶

Hematopoietic dysfunction in HIV-infected patients is well described and is likely multifactorial, resulting from direct suppression of progenitor cells by HIV, abnormal cytokine production, medications, opportunistic infection, malignancy, autoantibody production, and the stage of HIV infection.^{15,17}

Anemia: A potential role for erythropoietin

Recombinant erythropoietin has been used widely in the management of HIV-infected patients, particularly in association with zidovudine therapy, which may result in bone marrow suppression and anemia, especially at the higher doses that were common before the advent of highly active antiretroviral therapy.¹⁸ In recent reports of HIV/HCV-coinfecting patients treated with either nonpegylated or pegylated interferon and ribavirin, mean hemoglobin levels fell by as much as 2.3 g/dL¹⁹⁻²³ and 3.5 g/dL,²⁴ respectively, during the first 12 to 24 weeks of therapy, similar to the reductions seen in patients infected with HCV alone.

Preliminary studies suggest that, as in patients infected with HCV alone, recombinant erythropoietin may play a significant role in managing anemia during interferon/ribavirin therapy in patients coinfecting with HIV and HCV.^{24,25} In one study evaluating the use of interferon alfa-2b and ribavirin in 24 coinfecting patients,²⁵ hemoglobin decreased to less than 10 g/dL in 21% of patients. These patients were then treated with recombinant erythropoietin, and their mean hemoglobin level increased to 12.7 g/dL after 4 weeks, although 1 patient was unable to continue therapy because of persistent anemia. Another study,²⁴ still ongoing, is comparing the use of recombinant erythropoietin with ribavirin dose reduction in coinfecting patients who develop anemia during therapy with peginterferon alfa-2b and ribavirin. Patients who received recombinant erythropoietin have demonstrated increases in hemoglobin similar to those achieved by ribavirin dose reduction. These

findings suggest that the use of recombinant erythropoietin in coinfecting patients may improve our ability to continue ribavirin therapy at optimal doses in the setting of ribavirin-induced anemia.

Neutropenia: Preliminary evidence for a role for G-CSF

An important concern when treating patients coinfecting with HIV and HCV is the risk of interferon-associated neutropenia and lymphopenia, which could result in decreased CD4⁺ T-cell counts and potentially an increased risk of opportunistic infections. Lymphocytes may be reduced in up to 14% of patients infected with HCV alone who are treated with peginterferon and ribavirin.²⁶ Preliminary results indicate that CD4⁺ T-cell counts may decrease in HIV/HCV-coinfecting patients treated with either nonpegylated or pegylated interferon combined with ribavirin.^{19,21,23,27} However, the relative proportion of CD4⁺ T cells among total lymphocytes remains unchanged, the significance of which has yet to be established.

As a result of this potential risk, a CD4⁺ T-cell count of less than 100 cells/mL is a relative contraindication to interferon use, as interferon-induced decreases to this level have resulted in AIDS-defining opportunistic infections.²⁸ In coinfecting patients with CD4⁺ T-cell counts below 100 cells/mL, antiretroviral treatment should be prioritized in order to improve CD4⁺ T-cell counts before interferon is prescribed.²⁹ In coinfecting patients with normal CD4⁺ T-cell counts, the question of which disease to treat initially has not been resolved.

The use of G-CSF in HIV-infected patients has been shown to be effective and well tolerated.^{30,31} In patients coinfecting with HIV and HCV, preliminary findings suggest that G-CSF may be as effective as peginterferon dose reduction for the management of interferon-induced neutropenia.²⁴ Although these results appear promising for our ability to avoid potential dose reductions or discontinuation of peginterferon in coinfecting patients, further long-term studies will be required to validate them.

■ PATIENTS RECEIVING DIALYSIS FOR ESRD: ANEMIA IS THE CHIEF CONCERN

Chronic hepatitis C is a frequent problem in patients with ESRD, as 8% to 10% of hemodialysis patients in the United States have been exposed to HCV.^{32,33} Studies suggest that chronic hepatitis C is often relatively quiescent in ESRD patients,³³ but disease progression may accelerate after renal transplantation,³⁴ probably because of the immunosuppressive medications required. Overall, HCV-positive patients undergoing dialysis have higher mortality than HCV-nega-

tive ESRD patients,³⁵ and renal transplantation is beneficial in these patients. Thus, mild chronic hepatitis C is not a contraindication to transplantation.³⁶ Unfortunately, HCV infection is difficult to treat in patients after renal transplantation because of a substantial risk of graft rejection,³⁷ which makes clearance of HCV before renal transplantation highly desirable.

Ribavirin not recommended, interferon not well tolerated

Treatment of chronic hepatitis C in patients with ESRD is particularly challenging because ribavirin is considered contraindicated and because these patients have a reduced tolerance for interferon therapy.³³

Because ribavirin is cleared via renal excretion and only a small fraction is removed by dialysis, patients undergoing dialysis who are treated with ribavirin are at increased risk of severe hemolysis.³⁸ One recent study suggested that ribavirin may be given safely to these patients in low doses (< 300 mg/d).³⁹ In this study, patients received careful follow-up, monitoring of plasma ribavirin levels, and high-dose recombinant erythropoietin before and during therapy. Further studies of this nature will be required to enhance clinicians' confidence in the use of ribavirin in dialysis patients.

Because of the concerns about anemia, most studies in this population have used interferon alone, usually at a dose of 3 million units three times a week. Pharmacokinetic studies have shown that dialysis patients have higher peak and more sustained serum interferon levels than patients with normal renal function.⁴⁰ A meta-analysis of published trials that used interferon 3 million units three times a week demonstrated a higher rate of SVR in HCV-infected patients undergoing dialysis (33%)⁴¹ than was reported previously in large trials among patients with normal renal function who received interferon monotherapy (13% to 19%).^{42,43} At the same time, the incidence of adverse effects appears to be somewhat higher in patients undergoing dialysis. In HCV-infected patients with ESRD, interferon therapy should be strongly considered before renal transplantation, as evidence suggests that renal transplant recipients are at risk of having a severe, accelerated course of HCV-associated liver disease following transplantation while on immunosuppressants.³⁴

Anemia associated with renal failure occurs in virtually all patients with ESRD because of deficient renal production of erythropoietin. As a result, recombinant erythropoietin is widely used to treat anemia in patients with ESRD. Ribavirin is currently considered investigational for patients undergoing hemodialysis and cannot be recommended in routine practice. Whether the aggressive use of recombinant erythro-

poietin can allow for the safe use of ribavirin has yet to be demonstrated in controlled clinical trials.

Although anemia predominates as the major challenge facing dialysis patients receiving antiviral therapy for HCV infection, the usual precautions about reductions in the absolute neutrophil count and platelet count also apply.

■ LIVER TRANSPLANT RECIPIENTS: RECURRENT INFECTION IS COMMON, OFTEN SEVERE

HCV-associated liver disease is the leading indication for liver transplantation in the United States.⁴⁴ In liver transplant recipients who had chronic hepatitis C before transplantation, reinfection with HCV following transplantation is almost universal, and these patients are at risk of a severe, accelerated course of HCV-associated graft disease. In addition, recurrent chronic infection with HCV results in decreased patient and graft survival,⁴⁵ and the severity of recurrent liver disease is associated with the degree of immunosuppression required after transplantation.⁴⁶

The treatment of patients with recurrent HCV infection following liver transplantation is an area of great interest. Many concerns arise over the tolerability and efficacy of therapy with interferon/peginterferon and ribavirin in this population, as well as over the potential for graft rejection during therapy. Unfortunately, interferon monotherapy has shown minimal efficacy in transplant recipients with recurrent chronic hepatitis C, yielding SVR rates of less than 5%.^{47,48} Improved response rates have been observed with the combination of interferon and ribavirin, but efficacy is still poor compared with that in nontransplant patients. One recent study, for example, demonstrated SVR in 21% of liver transplant recipients with recurrent chronic hepatitis C treated with interferon and ribavirin.⁴⁹ In this study, 43% of patients discontinued therapy because of ribavirin-associated hemolytic anemia, and only dose reductions or discontinuation of treatment were used to manage adverse events. Others have observed similarly high rates of anemia in this population.⁵⁰⁻⁵²

The increase in ribavirin-associated hemolytic anemia in these patients may be associated with impaired renal function. Thus, ribavirin dosing in this population may need to be adjusted on the basis of weight and renal clearance to avoid dose reductions or discontinuation.⁴⁹

Preliminary results from a randomized trial in liver transplant recipients with recurrent HCV infection who were treated with peginterferon and ribavirin indicate that larger decreases in hemoglobin were associated with reduced renal clearance, suggesting

that preemptive therapy with recombinant erythropoietin may be important in maintaining adequate doses of ribavirin in these patients.⁵³ Additional studies using hematopoietic growth factors in liver transplant recipients will be required to determine any further benefit in adherence to and tolerance of therapy with interferon/peginterferon and ribavirin.

■ CONCLUSIONS AND IMPLICATIONS FOR THE FUTURE

Hematopoietic growth factors may offer a number of benefits to patients with chronic hepatitis C who are being treated with the combination of pegylated or nonpegylated interferon and ribavirin. These include improved tolerability of and adherence to combination therapy, a higher likelihood of completing a full course of therapy with minimal dose reductions, improved quality of life, and, potentially, prevention of infections. Growth factors may be of particular benefit in patient populations with impaired tolerability of combination therapy and complex treatment issues. Further studies will be required to validate the potential benefits of recombinant erythropoietin and G-CSF in these special populations and in all patients with chronic hepatitis C. It is likely that recombinant erythropoietin will be commonly used in these special populations and that recombinant G-CSF will have more limited use but still have a role in selected patients with severe neutropenia. A number of questions surrounding the use of growth factors have yet to be fully evaluated, including appropriate dosage, time of initiation, duration of therapy, impact on SVR, and cost-effectiveness.

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Managing the neuropsychiatric side effects of interferon-based therapy for hepatitis C

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■ ABSTRACT

Neuropsychiatric side effects are common with interferon-based therapy for chronic hepatitis C, and their prompt recognition and management is essential to effective patient care. Depression induced by interferon has been a significant cause of early treatment discontinuation in clinical trials. The need to monitor for and treat interferon-induced depression is well established, but whether to use antidepressants prophylactically remains controversial. Nonetheless, clinicians should maintain a low threshold for antidepressant therapy. Other significant neuropsychiatric side effects include anxiety, hypomania or mania, fatigue, and cognitive dysfunction. These can be additional sources of patient distress during interferon therapy and require appropriate intervention through patient education, psychotropic medications, support, and behavioral techniques.

Despite recent gains in the efficacy of antiviral regimens for the treatment of chronic hepatitis C, the tolerability of these regimens continues to be a significant problem. Neuropsychiatric side effects, such as depression, anxiety, mania, and fatigue, are especially common with regimens that include interferon alfa or pegylated

interferon alfa, and they contribute to the morbidity and mortality associated with these therapies for hepatitis C. Prompt recognition and management of these side effects is necessary to optimize patient safety and enhance treatment tolerability.

This article reviews the manifestations and management of depression and other neuropsychiatric side effects of interferon-based therapy, with the goal of helping physicians who treat patients with hepatitis C improve their overall patient management.

■ COMORBID PSYCHIATRIC AND SUBSTANCE ABUSE DISORDERS ARE COMMON WITH HEPATITIS C

Any discussion of the neuropsychiatric side effects of interferon therapy (which refers throughout this article to regimens including either conventional interferon alfa or pegylated interferon alfa) must consider the specific patient factors frequently associated with hepatitis C. Because illicit injection-drug use is a primary risk factor for infection with the hepatitis C virus, patients with hepatitis C often have a history of substance abuse. These patients also frequently have accompanying psychiatric illnesses, such as major depression, posttraumatic stress disorder, and personality disorders.

Because serious neuropsychiatric side effects (eg, severe depression, psychosis) have occurred in interferon-treated hepatitis C patients without a prior history of mental illness or substance abuse, concerns arose about the safety of interferon therapy in those with pre-existing psychopathology. These concerns led to recommendations not to prescribe interferon to this patient group, despite their high rates of hepatitis C.¹⁻³ Fortunately, recent experiences have shown that many of these patients can tolerate interferon therapy safely, without undue worsening of their psychiatric or substance abuse disorders.⁴⁻⁸ As a result, current recommendations call for patients to be considered on a case-by-case basis.⁹⁻¹¹ For many patients, close monitoring during interferon therapy and good coordination of care among hepatologists, mental health

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providers, and addiction specialists can yield successful treatment.

■ DEPRESSION IN INTERFERON-TREATED PATIENTS

When and how depression manifests

Depressive symptoms that arise during interferon therapy for hepatitis C have been a significant cause of premature treatment discontinuation in clinical trials. The precise prevalence of depression in interferon-treated patients with hepatitis C is unknown, owing to an abundance of confounding factors in clinical studies, such as differences in the diagnostic criteria and screening tools used to diagnose depression, whether or not preexisting depression has been present, and differences in the patient groups studied. Given these variations, the reported frequency of depression in interferon-treated patients with hepatitis C has ranged from 0% to 44%.

Risk factors for interferon-induced depression include the use of higher interferon doses, longer treatment duration, and the presence of subclinical depressive symptoms.^{12,13} Most often, depressive symptoms begin to develop within the first 12 weeks of interferon treatment and reach clinical significance in as little as 2 weeks.¹³ Because the incidence of depression is highest early in the course of therapy, patients should be monitored closely early in therapy using clinical interview and screening tools such as the Beck Depression Inventory (BDI), the Center for Epidemiologic Studies Depression Scale (CES-D), the Hamilton Depression Rating Scale (HAM-D), and the Montgomery-Asberg Depression Rating Scale (MADRS). In fact, the CES-D was validated for use among patients with chronic hepatitis C.¹⁴

Interferon-induced depression is considered a substance-induced mood disorder.¹⁵ Its symptoms are the same as those of major depression and include mood disturbance, apathy, anhedonia, fatigue, insomnia, anorexia, sexual dysfunction, and cognitive impairment. Suicidal ideation may be present but tends to be relatively infrequent. The accompanying mood disturbance may be described as feeling sad or "blue," but it may also consist of marked irritability. Because irritability also occurs with interferon-induced hypomania and mania, particular care is needed to distinguish which problem is present since antidepressants aggravate hypomanic and manic symptoms.

Etiology of interferon-induced depression

Various theories have been advanced about the etiology of interferon-induced depression, but the exact mechanism remains unclear. Interferon is known to

alter production of secondary cytokines, which in turn affects the central nervous system. In particular, increases in levels of the cytokines IL-6 and IL-8 have been linked to the development of interferon-induced anxiety and depressive symptoms.¹⁶ Secondary cytokines, which are also thought to affect the serotonergic system, are an area of interest because of their clear influence on psychiatric disorders. Animal studies have revealed reductions in serotonin and tryptophan levels in the brain following interferon exposure, while other studies have detected increases in serotonin reuptake mechanisms.¹⁶ Interferon also leads to depletion of tryptophan stores, the primary precursor of serotonin.¹⁷ Anxiety, depression, and cognitive disturbances associated with interferon therapy have been correlated with these reductions in tryptophan levels.¹⁷

Beyond influences on the serotonergic system, interferon also has effects on the hypothalamic-pituitary-adrenal (HPA) axis. Changes in the HPA axis have been linked to mood disorders and recently have been reported with interferon-induced depression.¹⁸ Patients who developed interferon-induced depression produced significantly elevated levels of cortisol and ACTH in response to initial doses of interferon, which suggests that there is an underlying vulnerability of the HPA axis in these individuals.¹⁸

Therapeutic strategies: To prevent or to treat?

While the importance of diagnosing and treating interferon-induced depression has been recognized, when to start antidepressant therapy is still debatable. Some studies support the prophylactic use of antidepressants for all patients receiving interferon for hepatitis C because of the frequency of interferon-induced depression.^{12,19} Most notably, one trial demonstrated a significant difference in the rate of depression among patients who received the selective serotonin reuptake inhibitor (SSRI) paroxetine prophylactically and those who did not.¹² Others have raised concerns about potential risks associated with antidepressant therapy, including retinal and gastrointestinal hemorrhage and stimulation of secondary mania.^{13,20} Instead, they recommend frequent monitoring of patients who are receiving interferon and prompt initiation of antidepressants once signs and symptoms of major depression arise.

Arguments can be made for either of these approaches, but further clinical studies are necessary. At this point, clinicians should maintain a low threshold for antidepressant therapy. Evidence of subclinical depression at the beginning of interferon therapy requires serious consideration of antidepres-

sants, given the increased risk of developing full-blown interferon-induced depression. Further decisions about early antidepressant use should take into account the patient's coping skills, support systems, and level of life stressors (eg, job setting, family duties, presence or absence of substance abuse) to determine whether mild mood symptoms from interferon therapy would be tolerable. Patients should be educated about the risks and benefits of prophylactic antidepressant therapy to allow them to play an active role in the decision whether to start medications.

SSRIs: The most-studied therapy option

Data on the treatment of interferon-induced depression has focused on SSRIs (Table 1), partly because of their ease of use and overall tolerability. More important has been the evidence suggesting that serotonin and tryptophan depletion may be the cause of interferon-induced mood disturbances. Sertraline, citalopram, fluoxetine, and paroxetine have all been reported to be effective in treating depression in interferon recipients,²¹⁻²⁷ and the latter two agents have also been given as prophylaxis for interferon-induced depression.^{12,28} Besides their utility as antidepressants, SSRIs also have demonstrated efficacy against symptoms of anxiety as well as a modest impact on alcohol consumption.²⁹ Not all interferon-induced neuropsychiatric symptoms respond equally to SSRI therapy, however, as anorexia and fatigue were noted in one study to be less responsive to paroxetine than were depression, anxiety, cognitive dysfunction, and pain.³⁰

Although SSRIs are generally considered safe, a recent report and a literature review have suggested that patients receiving both interferon and an SSRI may have an increased risk of retinal and gastrointestinal hemorrhage as well as cotton-wool spots.^{13,20} Since SSRIs can affect platelet function, concerns about their use in patients with hepatitis C who may have a tendency to bleed are not unfounded.

Evaluating other therapy options

Although experience in treating interferon-induced depression has focused on SSRIs, other antidepressants (Table 1) offer comparable efficacy and may be more helpful when certain interferon-related side effects are present.

Bupropion, for example, is a norepinephrine and dopamine reuptake inhibitor with activating qualities that may reduce the fatigue, psychomotor slowing, and cognitive impairment associated with interferon therapy. Bupropion also offers benefits for smoking cessation, which may be a consideration since tobacco

use may hasten liver fibrosis in hepatitis C.³¹ A small risk of seizures with bupropion use must also be taken into account, however, since interferon also can induce seizures.

Mirtazapine enhances both serotonergic and norepinephrine transmission, and it provides a more rapid onset of action than most antidepressants. Because of its antihistaminergic activity, mirtazapine tends to cause sedation as well as appetite increase and weight gain. These side effects can prove beneficial, however, when interferon-related insomnia and anorexia trouble patients. In rare cases, mirtazapine has been linked to agranulocytosis and severe neutropenia.³²

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor that may also offer a more rapid onset of action than most antidepressants. Its overall side-effect profile is similar to that of the SSRIs, though hypertension is an additional possibility. There have also been a limited number of case reports of hepatotoxicity.

Nefazodone, a serotonergic reuptake inhibitor and receptor antagonist, is an additional option for managing depression and anxiety. Because of its association with cases of acute hepatic failure, however, it is an unlikely choice for patients with chronic hepatitis C.

Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) are no longer first-line choices for treating depression or anxiety because of their side effects and potential for serious drug interactions. For patients with interferon-induced cognitive impairment, the anticholinergic effects of tricyclic antidepressants may cause further disturbances in cognitive function. MAOIs require a special diet along with avoidance of various medications. Additionally, while suicidal behavior tends to be infrequent in patients with interferon-induced depression, tricyclic antidepressants and MAOIs are more lethal in overdose than other antidepressants.

Psychostimulants such as methylphenidate or dextroamphetamine may offer an alternative approach for interferon-induced depression. Both of these psychostimulants have been used extensively in treating depression in the medically ill and in cases of treatment-refractory depression. Their onset of action is rapid, with improvements noted in as little as a few days to a week. Psychostimulants also offer benefits for reducing interferon-induced fatigue and cognitive dysfunction, as discussed below. Contraindications to the use of psychostimulants include a history of psychosis, tic disorders, uncontrolled hypertension, and tachycardia. Patients whose depression is accompanied by symptoms of anxiety may be unable to tolerate the

TABLE 1

Commonly used antidepressants and mood stabilizers that may help manage interferon-induced neuropsychiatric effects

Drug	Daily dosage (initial to maximum)	Comments
Antidepressants		
Selective serotonin reuptake inhibitors (SSRIs)		
Citalopram (Celexa)	10–60 mg	<ul style="list-style-type: none"> • General SSRI side effects include nausea, headache, jitteriness, sexual dysfunction, hyponatremia, reduced platelet function • Paroxetine can produce a discontinuation syndrome, so it should be tapered gradually
Escitalopram (Lexapro)	10–20 mg	
Fluoxetine (Prozac and others)	5–80 mg	
Fluvoxamine (Luvox and others)	25–250 mg	
Paroxetine (Paxil)	10–60 mg	
Paroxetine, controlled-release (Paxil CR)	12.5–62.5 mg	
Sertraline (Zoloft)	25–200 mg	
Bupropion, sustained-release (Wellbutrin SR)	100–400 mg	<ul style="list-style-type: none"> • Can be used for nicotine dependence • May lower seizure threshold • Not indicated for anxiety disorders
Mirtazapine (Remeron)	15–45 mg	<ul style="list-style-type: none"> • Antihistaminergic effects can counteract interferon-induced insomnia and anorexia
Venlafaxine (Effexor)	37.5–225 mg	<ul style="list-style-type: none"> • May increase blood pressure (dose-related) • Cases of hepatotoxicity reported
Psychostimulants		
Methylphenidate	5–60 mg	<ul style="list-style-type: none"> • Psychostimulants can also be helpful for fatigue or cognitive dysfunction • Psychostimulants have addictive potential
Dextroamphetamine	5–40 mg	
Mood stabilizers		
Valproate	250–3,000 mg	<ul style="list-style-type: none"> • Requires blood level monitoring
Lithium	150–1,200 mg	<ul style="list-style-type: none"> • Requires blood level monitoring
Carbamazepine	200–1,600 mg	<ul style="list-style-type: none"> • Requires blood level monitoring • May foster bone marrow suppression
Olanzapine (Zyprexa)	5–20 mg	<ul style="list-style-type: none"> • May foster glucose intolerance and hyperlipidemia

activating effects of these medications. Use of the psychostimulant pemoline is contraindicated for patients with hepatitis C because of the risk of hepatotoxicity.

■ ANXIETY: MANY SIMILARITIES WITH DEPRESSION

Symptoms of anxiety develop in approximately 10% to 20% of patients receiving interferon,³³ but it is unclear whether they are simply part of the presentation of interferon-induced depression or a separate phenomenon. Nonetheless, anxiety tends to develop shortly after interferon is started, and episodes of anxiety become more frequent and severe over time. The etiology of these anxiety symptoms appears to be similar to that of interferon-induced depression, as changes are noted in levels of serotonin, tryptophan, and cytokines.^{16–18}

Interferon-induced anxiety has been reported to respond to serotonergic antidepressants, but other antidepressants may also be effective. Benzodiazepines are another treatment option, offering more rapid anxiolysis. However, use of benzodiazepines in

patients with a history of substance abuse requires caution, owing to their addictive potential. Gabapentin, an antiepileptic agent that is not metabolized in the liver, has also demonstrated some anxiolytic properties and may be an additional choice for treatment of interferon-induced anxiety.³⁴

■ MANIA AND HYPOMANIA: GENERALLY A CAUSE FOR STOPPING INTERFERON

Interferon-induced mania and its milder presentation, hypomania, have been reported in a limited number of cases. In these cases, patients demonstrate excess energy, pressured speech, racing thoughts, marked distractibility, and increased goal-directed activity. When frankly manic, patients may also have paranoid or grandiose delusions and visual or auditory hallucinations. Accompanying mood disturbances include euphoria, expansiveness, irritability, and hostility. Hypomania and mania may develop a few weeks to several months after interferon therapy has

been initiated. Mania has also emerged following abrupt discontinuation of interferon or after a significant dose reduction. The etiology of interferon-induced mania remains unclear, but it may be related to dopamine hyperactivity or frontal cortical dysfunction. Less frequently, cases of interferon-induced psychosis have also been reported, although several included mood disturbances that suggested severe depression or mania.

In general, the management of hypomania or mania requires discontinuation of interferon, prompt psychiatric referral, and initiation of mood stabilizers (Table 1). Lithium, carbamazepine, and valproate are effective mood stabilizers that require careful monitoring of drug levels. With lithium, stable levels are difficult to maintain if fluid imbalance (ie, edema, ascites) or renal dysfunction is present. Potential side effects and drug toxicities must also be considered with these agents. Lithium-induced hypothyroidism and carbamazepine-induced neutropenia or thrombocytopenia may be a greater concern for patients already at risk for these side effects with interferon therapy. While valproate has raised fears about the risk of drug-induced hepatotoxicity, the recent literature suggests that safe use may be possible for patients with chronic hepatitis C.³⁵

Atypical antipsychotic agents are newer mood stabilizers that are likely to be the first choice for interferon-induced mania because of their ease of use, effectiveness, and tolerability. Unlike standard mood stabilizers, these agents do not require monitoring of serum drug levels and their dosing levels may be changed rapidly. Olanzapine has been the most studied of the atypical antipsychotics and has proven beneficial in treating manic episodes in patients with bipolar disorder at doses from 5 to 20 mg/d.³⁶ Quetiapine, risperidone, and ziprasidone are other atypical agents that can be used. Olanzapine is associated with an increased risk of glucose intolerance, which is a potential concern for patients with hepatitis C, since they have a higher than normal incidence of type 2 diabetes. On the other hand, the increased appetite and weight gain that are associated with olanzapine use may counteract interferon-related anorexia.

An alternative option for mood stabilization is gabapentin, given in doses from 900 to 1,800 mg/d. Successful control of interferon-induced mania was achieved at this dose range in a small series of patients with melanoma who received interferon alfa.³⁴ Besides providing mood stabilization, gabapentin was also believed to provide benefits as both an anxiolytic and a hypnotic.³⁴

■ FATIGUE: THE MOST COMMON SIDE EFFECT

Fatigue is the most common and troubling side effect of interferon because of its ability to interfere with daily functioning. Managing fatigue requires a multifaceted approach to address the loss of both physical and mental energy. Patient education about interferon-induced fatigue should alert patients to this complication and provide potential coping techniques (eg, flexible work hours, reassigning household responsibilities). Appropriate nutrition and rest should be encouraged. Nonpharmacologic techniques that are beneficial for cancer-related fatigue, such as energy conservation, moderate exercise, and restorative therapy, can be incorporated.

Beyond the use of recombinant human erythropoietin and thyroid hormone supplements, psychotropic medications offer additional options for treating fatigue. The psychostimulants methylphenidate (15 to 60 mg/d) and dextroamphetamine (10 to 40 mg/d) can be given in divided doses in the morning and at noontime.^{37,38} Both have been effective against fatigue related to cancer, HIV infection, and multiple sclerosis, but they must be used cautiously in patients with a history of substance abuse. Modafinil, a novel wake-promoting agent, has been helpful for treating fatigue in patients with multiple sclerosis. Small trials used doses of 100 to 300 mg/d and demonstrated good tolerability.^{39,40} Results from another trial suggest that carnitine supplementation (2 g/d) may reduce interferon-related fatigue in patients with hepatitis C.⁴¹ Carnitine's mechanism of action against fatigue is unknown but may be related to its effects on cellular energy metabolism.⁴¹

■ COGNITIVE DYSFUNCTION

Cognitive dysfunction is a less frequent side effect of interferon therapy, and studies have demonstrated changes suggestive of frontosubcortical impairment. Motor coordination, psychomotor speed, verbal memory, and executive function may be affected, though symptoms normally abate once interferon is stopped.

Interventions to reduce interferon-induced cognitive impairment are limited. Behavioral techniques used in early dementia, such as daily calendars and note-taking, may be helpful. Psychostimulants have improved cognitive function in patients with brain tumors or HIV infection by raising the level of alertness and enhancing attention and concentration.⁴² The opioid antagonist naltrexone has been used in a few cancer patients to reduce

interferon-induced neuropsychiatric symptoms; although some patients demonstrated improved cognitive function, tolerability was often a prob-

lem.⁴³ Additionally, a risk of hepatotoxicity reduces naltrexone's appeal for use in patients with hepatitis C.

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The role of physician extenders in managing patients with chronic hepatitis C

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■ ABSTRACT

The number of “physician extenders” (nurse practitioners and physician assistants) caring for patients with chronic hepatitis C is rising rapidly. Their growing role in the management of these patients promises greater efficiency in the delivery of care and more provider interaction with patients. This may yield benefits in terms of patient education and support, management of medication side effects, and patient adherence to treatment regimens. This article reviews the role of physician extenders in the management of patients with hepatitis C and outlines strategies for maximizing their contribution to the care of these patients.

The role of “physician extenders” (nurse practitioners and physician assistants) in primary care medicine and pediatrics has been extensively reported over the last 3 decades. However, literature on the role of physician extenders in subspecialty practices (including hepatology) is limited, even though the number of nonphysician personnel caring for patients with liver diseases is rising rapidly. This trend is evident in the management of patients with chronic infection with hepatitis C virus (HCV). There has been a sharp rise in the number of associate members of the American Association for the Study of Liver Diseases (AASLD) involved in patient care. This group includes registered nurses, nurse practitioners, and physician assistants. The AASLD’s associate

membership has more than quadrupled over a year and a half (from 39 in July 2002 to 173 in January 2004), and attendance at the AASLD Hepatology Associates Course rose from 272 in 2001 to 491 in 2003.¹

This article describes the role that physician extenders have increasingly assumed in the management of patients with chronic hepatitis C, and shares strategies for how physician extenders can best serve to improve the efficiency and quality of that management.

■ PHYSICIAN EXTENDERS: HOW THE CONCEPT EVOLVED

In response to the shortage and uneven distribution of primary care physicians in the mid-1960s, a group of health care professionals now known as physician assistants came into existence. Initially, this group consisted largely of Navy corpsmen, also called Medex, who had extensive military medical training.² In the next decade, Medex and physician assistants (PAs) were classified under the same category,³ and the 1970s also saw the advent of nurse practitioners (NPs) and nurse clinicians, who could deliver health care beyond the role of traditional registered nurses. PAs are licensed to practice medicine under the supervision of a physician,² whereas NPs may practice independently (in some states) or in partnership with other health care providers.⁴

The background, training, and certification requirements for the two professional groups also differ. NPs are registered nurses who receive 2 to 4 years of additional graduate nursing education, whereas PAs are graduates from a variety of disciplines who pursue at least 2 years of graduate education and training in primary medical care. NP certification is under the review of state boards of nursing, whereas state boards of medicine regulate the certification of PAs.

Despite these differences, the clinical roles of PAs and NPs overlap a great deal, justifying the combined designation “physician extenders.” NPs have been trained to provide care in acute, ambulatory, or long-term care settings.⁴ Their practice involves illness diagnosis and management, as well as health promotion and

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disease prevention. NPs may order, conduct, supervise, and interpret diagnostic tests, and they may prescribe certain medications. A major part of their practice is teaching and counseling individual patients, patients' families, and groups of patients. On the other hand, the comprehensive responsibilities of PAs include conducting physical examinations, illness diagnosis and treatment, ordering and interpreting diagnostic tests, counseling patients on preventive care, assisting in surgery, and, in most states, prescribing certain medications.²

■ HOW AND WHY PHYSICIAN EXTENDERS MATTER

Physician extenders have an important positive impact on the quality, efficient delivery, and cost of health care. Because additional medical personnel can accommodate more patients and allow for more time with patients, physician extenders enable increased patient access to care, increased patient time with a health care provider, decreased waiting time, and greater continuity of care.⁵ Physician extenders support efficient care delivery by attending to more minor and routine medical problems, allowing physicians to focus on cases requiring more expertise.³ In an organized health care system, this ability to deliver expanded services at a lower cost also represents a financial advantage to the organization, especially since physicians can devote themselves to more complicated (and more high-cost) services.² Indeed, the financial benefits of physician extenders include cost containment, increased reimbursement, increased physician productivity, and a partial solution to workforce shortages.⁵

■ CHIEF FUNCTIONS OF PHYSICIAN EXTENDERS IN HEPATITIS C

Physician extenders have assumed a number of important responsibilities in the management of patients with chronic HCV infection.^{6,7} These include:

- **Screening patients** with risk factors for HCV infection by ordering appropriate tests for HCV and excluding other causes of liver disease.
- **Taking detailed histories and performing comprehensive physical examinations.** This includes assessing for preexisting medical conditions, particularly depression, diabetes, heart disease, thyroid disease, and renal disease, and looking for signs of extrahepatic manifestations of hepatitis C and signs of cirrhosis or decompensated liver disease. These conditions have important implications for the treatment and monitoring of hepatitis C.
- **Educating patients and their families or partners about hepatitis C once the diagnosis is established.** This involves providing easy-to-understand infor-

mation on the disease process, its natural history, and modes of transmission. The education is based on the patient's level of understanding and readiness to learn. It extensively covers the side effects of medications prior to treatment, as well as how they are managed. Patients are taught the self-injection technique and are asked to do a return demonstration during the first session. Working step-by-step on issues in the treatment process enhances adherence and promotes successful disease management. For example, a simple phone call from the physician extender may strengthen the patient's rapport with his or her health care providers, enabling continuation of treatment despite difficult side effects.

- **Collaborating with specialists, the primary care provider, the patient, and other health professionals to manage treatment challenges.** Physician extenders may find that consultation with a psychiatrist or dermatologist is necessary to address side effects of therapy, and collaboration with a nutritionist may be needed to manage weight loss related to therapy or cirrhosis.
- **Closely monitoring patients in a standard-of-care or protocol setting.** Physician extenders look for treatment side effects that may be evident from the patient's symptoms, physical examination, or laboratory data.
- **Mentoring the nursing staff** involved in managing patients with hepatitis C, to optimize care delivery.

In addition to these specific functions, physician extenders can be instrumental in various quality management activities specific to hepatitis C, given their intimate involvement in care delivery. Physician extenders also increasingly contribute to the general knowledge base in hepatitis C through participation in clinical research, contributions to scholarly works, presentations at professional and continuing education meetings, and active participation as associate members of the AASLD. Although certification for physician extenders in the subspecialty of hepatology is desired, it has not yet been put in place. Such certification would enable physician extenders to stay on the cutting edge of current treatments and better learn from their peers in hepatology.

■ STRATEGIES USED BY PHYSICIAN EXTENDERS FOR ENHANCING PATIENT MANAGEMENT

As previous articles in this supplement have made clear, managing patients with hepatitis C involves overcoming many challenges, such as the difficulty of ensuring adherence to treatment, the wide spectrum of treatment side effects, and the tendency for many

HCV-infected patients to have psychosocial or financial challenges. Physician extenders are well suited to play a prominent role in efforts to overcome these challenges, with the goal of enhancing adherence to therapy and thereby optimizing therapeutic outcomes (Figure 1). This section details specific strategies that physician extenders can and do employ to overcome these challenges and improve patient management.

Identifying sources of social and financial support

Physician extenders are well positioned to help patients take advantage of their social support system, ie, family members, friends, community and church groups, and coworkers. This often includes identifying persons who can provide financial assistance, coordinate clinic visits, and help handle other practical matters. Physician extenders also frequently counsel patients on whether they may need a more flexible work schedule and assistance with household chores during their treatment. Similarly, they may need to discourage patients from starting a new job, business, or personal pursuit that could produce additional stress during therapy.

Because financial stability can be a stressful issue, physician extenders should be prepared to present and explain relevant worker-protection laws, such as the Family and Medical Leave Act and the Americans with Disability Act, if warranted. Discussion of the patient's financial resources may reveal a need to coordinate the source of payment for office visits, medical consultations, laboratory tests, and medications. The patient also should be made aware of industry-sponsored programs or specialty pharmacies that may provide assistance with medications on the basis of financial need.

Educating and empowering patients

The patient's level of education affects his or her understanding of hepatitis C and its management, especially antiviral therapy. The use of simple language without jargon can be key in explaining the medication regimen. By determining the patient's level of understanding of HCV infection and any preliminary information on the disease, the physician extender is able to appropriately build on that knowledge base. Patients can also be directed to reliable sources of information such as the National Institutes of Health, the Centers for Disease Control and Prevention, the American Liver Foundation, and the Hepatitis Foundation International.

Patient education must continue throughout therapy. It should elaborate on the natural history and prognosis of the disease, emphasizing modes of transmission and risk reduction as well as ways to improve general well-being (eg, increasing hydration, exercise, good

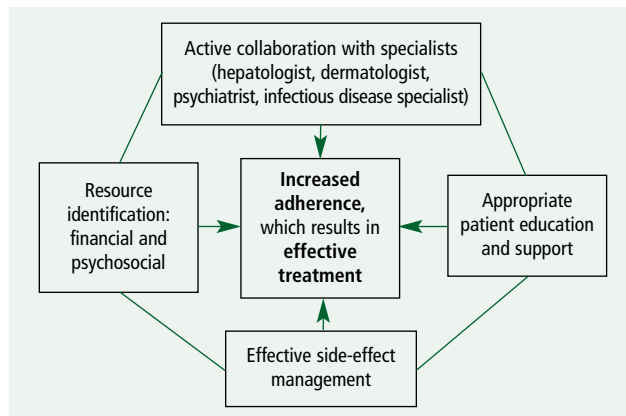


FIGURE 1. Major contributions of physician extenders to the management of patients with chronic hepatitis C.

nutrition, avoiding alcohol). Medication adherence also must be emphasized—specifically, maintaining more than 80% of the dosage of the drugs for more than 80% of the time to improve early virologic response and to enhance sustained virologic response.⁸ Treatment-naïve patients require more information and support to deal with medication side effects.

All patients should be encouraged to take ownership of and accountability for their own care. All are asked to abstain from alcohol to improve their response to treatment, and cirrhotic patients require strict abstinence. Physician extenders should encourage participation in patient support groups, which can be extremely helpful. They also should provide ample opportunity for patients to ask questions and clarify myths. Knowledge is empowering: the more knowledge patients have, the more likely they are to adhere to treatment.

Managing side effects of combination antiviral therapy

A 2002 National Institutes of Health consensus conference on hepatitis C concluded that combination therapy with pegylated interferon alfa (peginterferon) and ribavirin results in the highest response rates of any therapy for chronic hepatitis C.⁹ However, this combination can result in nonspecific, systemic, hematologic, neuropsychiatric, reproductive, cardiovascular, respiratory, dermatologic, and gastrointestinal side effects (Tables 1 and 2) that require effective management to ensure adherence to treatment. These side effects may diminish patients' quality of life¹⁰ and reduce their productivity. Side effects are most intense during the initial few months of therapy. It is crucial that patients anticipate these side effects in an attempt to minimize them and to implement interventions to manage them.

Because of this wide spectrum of side effects and the long duration of therapy for chronic hepatitis C, close

TABLE 1

Practical strategies for managing side effects of combination therapy in patients with chronic hepatitis C*

Side effects caused by pegylated interferon	Side effects caused by ribavirin
<p>Flulike symptoms (fever, chills, myalgia, and headache are most common)</p> <ul style="list-style-type: none"> • Thoroughly educate and prepare patient for these symptoms • Advise patient to take injection 2 to 3 hours before bedtime • Advise patient that he/she may premedicate with acetaminophen or an NSAID (and may repeat as directed), but patients with cirrhosis should avoid NSAIDs • Ensure adequate hydration (weight in kg = ounces of noncaffeinated fluids) • Suggest that warm blankets may help with chills <p>Fatigue</p> <ul style="list-style-type: none"> • Assess at baseline and at follow-up visits. Exclude organic and psychiatric causes of fatigue (anemia, hypothyroidism, depression, etc). • Encourage efforts to continue to work • Advise that mild activity (eg, walking, swimming) can help reduce stress • Tell patient to “listen to your body” and take breaks when possible • Suggest taking one or two naps during the day • Advise patient to delegate tasks if possible (eg, ask family or friends to do laundry) • Advise patient to eat at regular intervals for adequate energy <p>Neuropsychiatric side effects[†]</p> <p><u>Depression/mood disturbance</u></p> <ul style="list-style-type: none"> • Obtain a baseline assessment for depression • If a patient is depressed or has a history of depression, consider antidepressants • Investigate and manage other neuropsychiatric side effects (anxiety, mania, etc) • Encourage patient to consider support groups or relaxation techniques • If symptoms do not improve, refer to a psychiatrist <p><u>Headaches</u></p> <ul style="list-style-type: none"> • Assess for various etiologies (eg, migraine, allergy status, hydration, drug interaction, infection, insomnia) • Thorough neurologic exam warranted. Refer to neurologist if headaches worsen. • Advise patient to avoid alcohol and caffeinated beverages <p><u>Insomnia</u></p> <ul style="list-style-type: none"> • Advise patient to maintain good sleep hygiene and stay awake during the day • Suggest light exercise during the day • Suggest that patient drink a warm glass of milk at bedtime • Evaluate for depression • Consider use of mild sedatives <p><u>Impaired concentration</u></p> <ul style="list-style-type: none"> • Provide reassurance (“It’s usually temporary.”). Involve family members if needed. • Advise patient to make lists and check off completed tasks • Suggest keeping a diary and writing notes to self • Advise patient that short naps may help 	<p>Cough (generally nonproductive)</p> <ul style="list-style-type: none"> • Assess at baseline and monitor thereafter • Investigate for infection or allergy • Suggest a humidifier or hard candy • Encourage smokers to quit smoking • If worsening or severe, exclude other causes (pulmonary fibrosis, cardiac, etc) <p>Rash/dry skin/itching</p> <ul style="list-style-type: none"> • Perform baseline and subsequent skin assessments. Consider extrahepatic manifestation of HCV infection. • Suggest tepid showers or baths, followed by patting the skin dry • Advise keeping skin well moisturized. Suggest soaps with moisturizers, sunscreen, products for sensitive skin. • Consider topical antipruritics, such as diphenhydramine cream • Use hydrocortisone ointment sparingly • Suggest oatmeal baths to ease itching • Consider dermatology consult for uncontrolled rash <p>Teratogenic/embryocidal effects</p> <ul style="list-style-type: none"> • Require patient to practice two methods of contraception during treatment and 6 months thereafter • Do baseline and monthly pregnancy tests for women of childbearing age

* Adapted in part from “Guiding Patients Through Chronic Hepatitis C Therapy,” Schering Hepatitis Innovations, Schering Corp., Copyright © 2002.

† Refer to article by Crone and colleagues in this supplement for more detail on management of these side effects.

monitoring and continued support of patients is essential to maintaining adherence. Physician extenders can facilitate simple interventions that may ameliorate some of these side effects. When gastrointestinal symptoms such as nausea, diarrhea, anorexia, or dyspepsia occur, patients should be encouraged to avoid fatty and spicy foods, follow the “BRAT” (banana, rice, apple-sauce, toast) diet, try ginger tea or candy, and eat small but frequent meals. For alopecia, patients can be advised to avoid harsh hair treatments, wear hats or

hairpieces, or use hair products that minimize hair loss. If a patient has diarrhea, stool examinations should be done to rule out infection. If chest pain or palpitations occur, a cardiology evaluation is mandatory.

Cytopenias are a common challenge during treatment. Approximately 10% of patients experience reversible hemolytic anemia from ribavirin therapy, and interferon or peginterferon therapy may induce anemia and neutropenia. According to the package insert for ribavirin, the dose should be reduced if the patient’s

hemoglobin falls below 10 g/dL and the drug should be permanently discontinued if the hemoglobin falls below 8.5 g/dL. However, the use of erythropoietic growth factors (epoetin alfa or darbepoetin alfa) may allow clinicians to manage anemia proactively. These growth factors may increase hemoglobin levels and thus improve anemia-related symptoms and health-related quality of life, as reported in several studies detailed by Ong and Younossi earlier in this supplement.

Neutropenia and thrombocytopenia have also been noted in HCV-infected patients receiving combination antiviral therapy. Neutropenia is more frequent than thrombocytopenia, although the latter is more pronounced in patients with cirrhosis. Both of these side effects may require antiviral dose reduction, which may have implications for the likelihood of sustained virologic response, but their management varies. Some clinicians use growth factors such as filgrastim (granulocyte colony-stimulating factor) to treat neutropenia,¹¹ although it is not currently approved for use in HCV-infected patients receiving interferon or peginterferon. Other clinicians may accept lower neutrophil counts and prefer close monitoring over peginterferon dose reduction. However, unlike in patients with chemotherapy-induced neutropenia, evidence of an increased risk of infections among patients with hepatitis C is currently lacking. Oprelvekin (IL-11) has not been accepted with any enthusiasm for thrombocytopenia related to hepatitis C therapy, owing to its high incidence of side effects. Moreover, thrombocytopenia-related bleeding episodes are not common.

The exact role of physician extenders in managing cytopenias in HCV-infected patients depends on the practice setting. Large centers may have protocols in place for consideration of hematopoietic growth factors for anemia and neutropenia. In such a setting, physician extenders can follow the protocol established by a multidisciplinary team. Indeed, it has become increasingly necessary that physician extenders follow established protocols or seek the advice of the treating physician before reducing the dose of antiviral therapy.

SUMMARY

Over the past 3 decades, physician extenders have become increasingly involved in subspecialty practices such as hepatology, and particularly in the management of patients with hepatitis C. In general, their roles include diagnosis and disease management, health promotion, and disease prevention. Physician extenders' participation in hepatitis C management and active collaboration with clinical specialists may help to ensure adequate patient education, better

TABLE 2
Practical strategies for managing cytopenias due to combination therapy for chronic hepatitis C*

Anemia (caused by ribavirin and interferons)

- Take complete blood cell count at baseline, at weeks 2 and 4 of therapy, and monthly thereafter
- Discuss with patient the signs and symptoms of anemia, including fatigue, shortness of breath, etc
- Instruct patient to notify provider if dyspnea develops
- Consider use of epoetin alfa or darbepoetin alfa

Neutropenia (caused by interferons)

- Advise frequent hand-washing
- Advise avoidance of crowds
- Consider use of granulocyte colony-stimulating factor

Thrombocytopenia (caused by interferons)

- Advise use of a soft-bristled toothbrush
- Discourage shaving of large areas; urge use of electric razor
- Suggest use of a humidifier to keep nasal mucosa moisturized and to minimize nose bleeds
- Instruct patient to notify provider of any signs of bleeding and to seek emergency treatment if uncontrolled

* Refer to article by Ong and Younossi in this supplement for more detail on management of these hematologic abnormalities.

identification of resources for patients, and effective management of medication side effects. In these ways, physician extenders can facilitate patient adherence to therapy, which is crucial for enhancing the efficacy of treatment for hepatitis C.

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