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

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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.

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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

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 pharmakokinetic 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 glygol (PEG) to the interferon molecule in either a liner 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 trials[4–6] have evaluated virologic response to peginterferon and ribavirin in previously untreated patients with chronic hepatitis C.

The first trial[4] 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 trial[6] 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 results[6] 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 study[4] 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 $\log_{10}$ 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 therapy was less than 80% of the expected duration, the chance of an eventual SVR in these patients was only 50%.

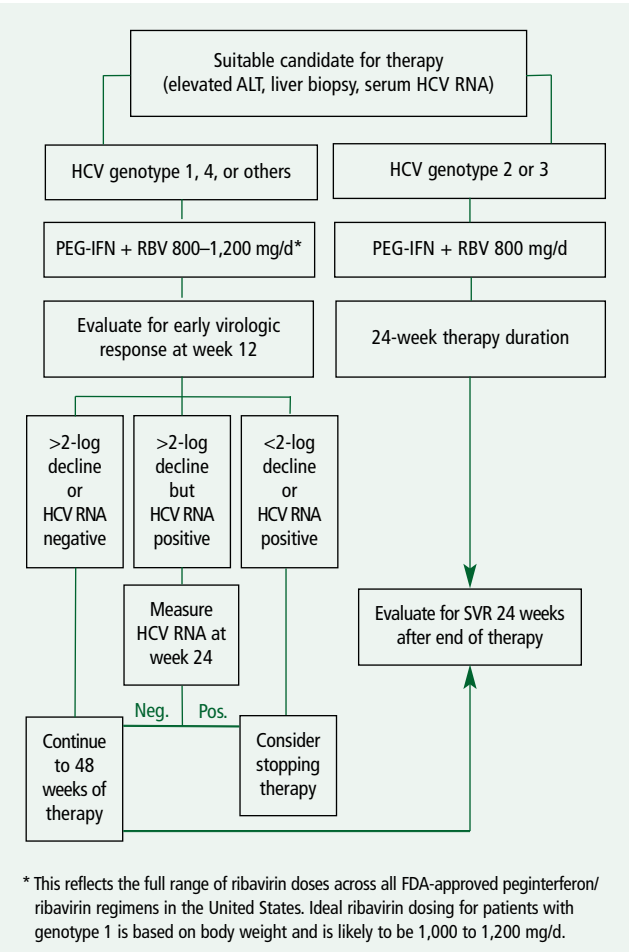

FIGURE 1. Treatment algorithm for previously untreated patients with chronic hepatitis C virus (HCV) infection (ALT = alanine aminotransferase; PEG-IFN = pegylated interferon; RBV = ribavirin; SVR = sustained virologic response).

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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