

Retreatment of Patients With Chronic Hepatitis C

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Significant advances have been made in the treatment of chronic hepatitis C virus (HCV) infection during the past 5 years. As a consequence, there is continuing enthusiasm for retreating patients who did not achieve sustained virological response (SVR) with previous therapy. Retreatment of non-responders to standard interferon monotherapy using interferon and ribavirin has yielded SVR rates of 12% to 15%. Retreatment with peginterferon and ribavirin has been more effective; achieving SVR rates of 34% to 40%. Retreatment of patients who relapsed after interferon monotherapy using standard interferon and ribavirin yielded SVR rates of 47%, whereas retreatment with peginterferon and ribavirin resulted in an SVR rate of about 60%. The major factors associated with a higher likelihood of an SVR after retreatment include previous relapse, previous treatment with interferon monotherapy, HCV genotypes 2 or 3, lower serum levels of HCV RNA, and having a significant decrease in HCV RNA levels during the initial course of therapy. These results help to focus retreatment with peginterferon and ribavirin on subsets of patients who are most likely to benefit. (HEPATOLOGY 2002;36:S128-S134.)

Since the first National Institutes of Health Consensus Development Conference on the "Management of Chronic Hepatitis C" in March 1997, the success rates of therapies for chronic hepatitis C have improved significantly.¹ The 1997 Consensus Panel recommended standard interferon alfa in a dose of 3 million units (MU) 3 times weekly for 48 weeks as the optimal therapy for chronic hepatitis C. Unfortunately, the sustained virological response (SVR) rate of a 48-week course of interferon monotherapy was only 12% to 16%, and rates were even lower in selected cohorts such as African Americans and patients with hepatitis C virus (HCV) genotype 1.^{2,3} At the time of the initial Consensus Conference, only preliminary data were available on the effectiveness of interferon and ribavirin combination therapy.⁴ Shortly thereafter, several large clinical trials demonstrated the superiority of combination therapy over interferon

monotherapy,^{2,3} and in 1998, this regimen was approved by the U. S. Food and Drug Administration (FDA) for treatment of chronic hepatitis C. The combination of interferon alfa (3 MU 3 times a week) and ribavirin (1,000 to 1,200 mg daily) for 24 to 48 weeks yielded SVR rates between 36% and 47%, 2-fold to 3-fold higher than that observed with interferon monotherapy. More recently, pegylated interferons (alfa-2a and alfa-2b) have been developed, and 2 large clinical trials using peginterferon and ribavirin yielded SVR rates of 54% to 56%, which were 7% to 12% higher than those achieved with standard interferon and ribavirin.^{5,6} Peginterferon alfa-2b and ribavirin was approved by the FDA for the treatment of chronic hepatitis C in 2001. The approval of peginterferon alfa-2a is anticipated in the near future.

With the introduction of each new, more effective therapeutic regimen for hepatitis C, the issue of retreatment arises. The major rationale for retreatment has been that a more effective regimen is likely to lead to an SVR in at least a proportion of patients who failed to respond to the previous, less effective regimen. Unfortunately, preliminary studies have demonstrated that the overall rates of response during retreatment tend to be limited. Several clinical and virological factors can be helpful in predicting the likelihood of a response to retreatment and higher response rates can be achieved by carefully selecting patients for retreatment. Only prospective trials can address the issue of whether retreatment is beneficial and for which groups of patients.

This review is based on the published and emerging data regarding the effectiveness of retreating patients who

Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response; MU, million units; ALT, alanine aminotransferase; FDA, Food and Drug Administration.

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have failed to respond to previous treatment for chronic hepatitis C and our current understanding of the response rates to combination therapy with peginterferon and ribavirin. Because peginterferon has only recently been introduced, there is little information on the effectiveness of retreatment using this product. The bulk of published studies on retreatment are based on use of combination therapy with standard interferon and ribavirin in patients who previously received interferon monotherapy. The lessons learned from that experience are applicable to the issue of combination therapy with peginterferon and ribavirin.

Categories of Patients for Retreatment

Patients being considered for retreatment can be categorized into 2 groups: relapsers and non-responders. Relapsers are patients who become HCV RNA negative during a course of therapy, but then relapse and redevelop HCV RNA after stopping treatment. Non-responders are patients who do not become HCV RNA negative during therapy. These definitions require regular timed testing for HCV RNA using a sensitive and reliable method. A third pattern of response is referred to as breakthrough, in which patients become HCV RNA negative initially and then redevelop HCV RNA while still receiving therapy. Patients with this pattern are identified only by repeat HCV RNA testing during therapy and for general discussion should be considered non-responders. Examples of the different patterns of response are shown in Fig. 1.

The definitions for responses to therapy of hepatitis C were initially delineated at the first Consensus Develop-

Table 1. Factors to Consider When Assessing the Usefulness of Retreatment

The efficacy of the previous therapy
The efficacy of the therapy to be used for retreatment
The character of the response to previous therapy
Race
HCV genotype
Severity of liver disease
The ability to tolerate and/or comply with the previous and current therapy
Ongoing alcohol consumption

ment Conference on management of hepatitis C.⁷ At that time, responses were categorized as biochemical, virological, or histological, and as either end-of-treatment or sustained. At the time of the previous Consensus Conference, tests for HCV RNA had only recently been introduced, and these assays were neither standardized nor universally applied. In some instances, HCV RNA testing was not performed, and in others the tests utilized to detect HCV RNA were not always sensitive or reliable. For these reasons, responses to therapy were sometimes assessed based on serum alanine aminotransferase (ALT) levels, and in many retreatment studies, only biochemical response rates were reported. In recent years, it has become clear that virological response rates are more predictive than biochemical responses of both short-term and long-term outcome.⁸ Sensitive and specific assays for HCV RNA are now widely available, and current definitions for relapse and non-response are generally based on virological criteria alone.

Within the group of non-responders are 2 different virological patterns of response (Fig. 1). A proportion of patients have little or no decrease in HCV RNA levels during therapy, the decrease being less than 2 log₁₀ units (null or flat response). In another proportion, serum HCV RNA levels decrease at least 2 log₁₀ units, but still remain detectable during therapy (partial response). The differences between these 2 patterns may be important, as patients with a significant decrease in HCV RNA levels may have improvements in serum ALT levels and hepatic histology, as well.^{9,10} These patients may also have a greater likelihood of achieving a SVR when retreated with a more effective therapeutic regimen.¹¹

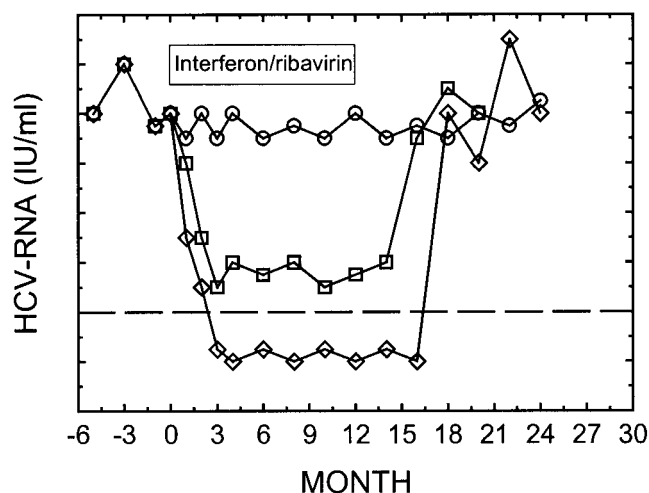


Fig. 1. Graphic representation of the various patterns of response in patients with chronic hepatitis C treated with interferon alone or the combination of interferon and ribavirin for 48 weeks. Relapse (◇), null-response (○), partial virological response (□). The thick dashed line represents the lower limit of detection for HCV-RNA.

Factors That Correlate With a Response to Retreatment

Several factors are important in the decision to recommend retreatment (Table 1). The major predictive factors for an SVR with retreatment are the type of responses that occurred with the previous course of therapy and the difference in efficacy between the initial and the repeat

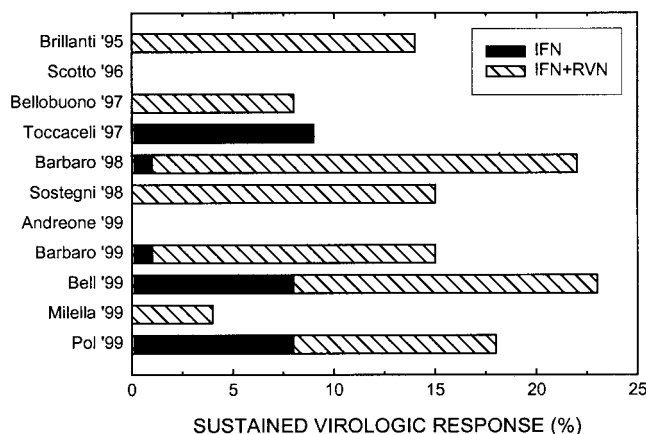


Fig. 2. Summary of the reported rates of SVR from several studies in which interferon non-responders were retreated with either interferon monotherapy (IFN) or interferon and ribavirin (IFN + RVN). Data from Cummings et al.¹³

course of treatment. Several studies have shown that re-administration of the same regimen of therapy is unlikely to be beneficial, unless the previous course was stopped early or was not adequately administered. New treatment regimens have utilized higher doses of interferon, a different type of interferon, a longer duration of therapy, or the addition of a second medication, such as ribavirin and its dose and duration of treatment. The likelihood that retreatment will be successful is directly related to the differences in efficacy between the initial and the retreatment regimens.

The most information available on retreatment is from studies of combination therapy using interferon and ribavirin in patients who previously received interferon monotherapy. There have been 2 meta-analyses of retreatment in this situation.^{12,13} Among non-responders, retreatment with the same dose-regimen of interferon resulted in an SVR in less than 5% of patients; and in several studies, no non-responder patient treated with the

same regimen had an SVR (Fig. 2). Similar data were observed for relapser patients. Although about half of relapsers had an end-of-treatment response when retreated with the same regimen, relapse was again common and SVR rates were less than 5%.¹⁴ Thus, an important component of retreatment is that the regimen used is more effective than the initial treatment.

The range of responses and sustained responses reported for the various therapies currently available for treatment and retreatment of chronic HCV infection are listed in Table 2. The expected range for SVR during retreatment can be estimated by calculating the difference in end-of-treatment virological response rates between the 2 therapies and the relapse rate of the newer treatment. For example, patients who were non-responders to interferon monotherapy (which has an end-of-treatment-response rate of 24% to 29%) would be expected to have a 21% to 37% chance of an end-of-treatment response to interferon and ribavirin (which in naïve subjects has an end-of-treatment-response rate of 50% to 61%). These same non-responders to interferon monotherapy would have a 36% to 54% chance of an end-of-treatment response to peginterferon and ribavirin (which in naïve subjects has an end-of-treatment response rate of 65% to 68%). In contrast, patients who failed to respond to interferon and ribavirin would have only a 21% to 37% chance of responding to peginterferon and ribavirin. Because relapse rates to combination therapy have averaged 20%, the expected range for SVR after retreatment can also be calculated. The actual sustained response rates observed during retreatment studies were well within what would be expected based on these calculations.^{12,13}

An often overlooked, but critically important factor, in predicting response during re-treatment is the quality of the response during the previous course of therapy. As noted above, 3 types of virological patterns occur in patients who failed to achieve an SVR: relapse, the null or

Table 2. Calculated Rate of Response After Retreatment of Non-Responders

Initial Course of Therapy		Retreatment Course		
Regimen	On-Treatment Virological Response (%)	Regimen	On-Treatment Virological Response§ (expected) (%)	Sustained Virological Response (expected) (%)
Standard interferon*	24-29	Interferon and ribavirin	21-37	11-19
		Peginterferon and ribavirin	36-54	29-43 (36)
Standard interferon and ribavirin†	50-61	Peginterferon and ribavirin	3-18	2-14 (8)
Peginterferon and ribavirin‡	65-68			

*Interferon alfa-2b 3 MU 3 times weekly.

†Interferon alfa-2b 3 MU 3 times weekly and ribavirin 1,000 to 1,200 mg/d.

‡Peginterferon alfa-2b 1.5 μ g/kg/wk and ribavirin 800 mg/d or peginterferon alfa-2a 180 μ g weekly and ribavirin 1,000 to 1,200 mg/d.

§Expected virological response was calculated by subtracting the on-treatment response of the initial and retreatment therapies.

||Calculated by assuming a 20% relapse rate after combination therapy with peginterferon and ribavirin.

flat response, and a partial virological response (Fig. 1). Nearly all patients with prior relapse will again become HCV RNA negative when retreated with a more effective therapy. However, these patients still can relapse again after retreatment. The rate of SVR in relapsers correlates, at least in part, with HCV genotype and pretreatment HCV RNA level.¹⁴ For non-responders, those with a partial virological response during their initial treatment appear more likely to achieve an SVR during retreatment. Indeed, in one study in which patients were retreated with combination interferon and ribavirin, SVR was observed only in those patients who had a decrease in the serum HCV RNA level to less than 100,000 copies/mL using the Amplicor competitive polymerase chain reaction method (Roche Diagnostics, Nutley, NJ) during the initial course of interferon monotherapy.¹¹ Unfortunately, data regarding changes in HCV RNA levels during the initial treatment were not available in nearly all of the other published retreatment trials.

Other factors, which affect the response to retreatment, include patient tolerance and compliance. Patients who have moderate to severe side effects and who require interferon or ribavirin dose reduction or drug discontinuation are likely to have similar problems with retreatment, unless the side effects can be successfully treated. Approaches to better management of side effects that might allow continuation of therapy are addressed elsewhere in these proceedings.¹⁵ Alcohol use may also contribute to non-response or relapse after therapy of hepatitis C.¹⁶ Thus, abstinence from alcohol may improve response rates to therapy and should be encouraged in all patients with hepatitis C, particularly those receiving interferon.¹⁷

Retreatment of Non-Responders

The retreatment of interferon non-responders with interferon and ribavirin has been the subject of several publications including 2 meta-analyses and a recent review.^{12,13,18} The number of patients evaluated in these studies ranged from 14 to over 300. Overall, these reports represent the retreatment of over 1,000 interferon non-responders. The majority of these studies utilized biochemical criteria to define non-response. The patients were retreated for either 24 or 48 weeks and followed for an additional 24 weeks after discontinuation of therapy and the dose of ribavirin varied from 600 to 1,200 mg/d. Despite variations in the inclusion criteria, study design, and the dose and duration of interferon and/or ribavirin among these studies, the results were generally consistent. On average, 26% to 32% of interferon non-responders became HCV RNA negative when retreated with interferon and ribavirin. SVR rates ranged widely, from 0% to

21%, but in most studies, rates were 12% to 15%. These values were well within the estimated rates of response to retreatment (Table 2). Higher response rates to retreatment were associated with HCV genotype non-1, treatment duration of 48 rather than 24 weeks, lower baseline HCV RNA levels, non-black race, absence of cirrhosis, use of standard doses of ribavirin (1,000 to 1,200 mg/d), and previous partial virological response to interferon monotherapy.^{11,12,18}

Peginterferon has only recently been available for the treatment of patients who were non-responders to either interferon or interferon and ribavirin. Preliminary results are available from only 2 studies, both of which are still ongoing.^{19,20} In one study, 17 non-responders to interferon monotherapy and 84 non-responders to interferon and ribavirin, all of whom had HCV genotype 1, were retreated with either peginterferon alfa-2b (1.0 μ g/kg/wk) and the standard dose of ribavirin (1,000 to 1,200 mg/d) or peginterferon alfa-2b (1.5 μ g/kg/wk) and a lower dose of ribavirin (800 mg/d). Overall, SVR occurred in 25% of patients treated with the higher dose of interferon and the lower dose of ribavirin and in 40% of patients treated with the lower dose of interferon and higher dose of ribavirin. As would be expected, patients who were non-responders to previous treatment with combination therapy fared less well, SVR rates being 10% to 11%.

In another multicenter study, 212 non-responders to either interferon monotherapy or interferon and ribavirin were retreated with peginterferon alfa-2a (180 μ g/wk) and the standard dose of ribavirin (1,000 to 1,200 mg/d). All patients included in this trial had advanced fibrosis or cirrhosis, and 88% had HCV genotype 1. Of those patients who had previously received interferon monotherapy, 53% responded to retreatment, and 34% achieved an SVR. In contrast, 30% of non-responders to interferon with ribavirin became HCV RNA negative, and only 11% achieved an SVR. These rates were within the range predicted by comparing the results observed for these therapies in naïve populations (Table 2). SVR was observed in only 15% of patients with HCV genotype 1 compared with 60% for patients with HCV genotypes 2 or 3. Only 11% of African Americans became HCV RNA negative during retreatment with peginterferon and ribavirin, but none achieved an SVR.

These preliminary results suggest that approximately 25% to 40% of non-responders to interferon monotherapy will achieve an SVR with peginterferon-ribavirin combination therapy, but only 10% to 11% of non-responders to standard interferon-ribavirin combination therapy have a sustained response to retreatment with peginterferon-based combination therapy.

Retreatment of Relapsers

The combination of interferon and ribavirin was initially approved by the FDA for retreatment of patients with chronic HCV who relapsed after treatment with interferon monotherapy. In the first large multicenter study to demonstrate the efficacy of interferon and ribavirin for this indication, patients were randomized to retreatment with either interferon monotherapy (3 MU 3 times a week) or interferon and ribavirin (1,000 to 1,200 mg /d).¹⁴ All patients were treated for 24 weeks and followed for an additional 24 weeks. Only 49% of relapsed patients retreated with interferon monotherapy became HCV RNA negative, and the SVR rate was only 5%. In contrast, 82% of patients retreated with the combination of interferon and ribavirin became HCV RNA negative, and 47% achieved an SVR. Factors that correlated with an SVR in response to retreatment were genotypes 2 or 3 and baseline serum levels of HCV RNA less than 2 million copies/mL. An SVR occurred in 95% of patients with both of these favorable factors.

In a second study, patients who relapsed after treatment with interferon monotherapy were retreated with interferon (3 MU 3 times a week) and ribavirin (1,000 to 1,200 mg/d) for 24 weeks and were then randomized either to stop both drugs or to continue ribavirin as monotherapy for an additional 24 weeks.²¹ HCV RNA became undetectable in 74% of patients during retreatment, and SVR occurred in 56%. There was no additional benefit of continuing ribavirin monotherapy.

Data regarding the effectiveness of peginterferon and ribavirin for retreatment of patients who relapsed after initial treatment with interferon and ribavirin are available only from a single study, which is still ongoing.¹⁹ Of 15 patients retreated with peginterferon alfa-2b at a dose of 1.5 μ g/kg/wk and ribavirin 800 mg/d, 87% achieved an end-of-treatment response and 60% an SVR. The effect of continuing therapy for a longer period of time requires further study.

Appropriate Candidates for Retreatment

The recent increase in response rates to treatment with peginterferon and ribavirin in chronic hepatitis C has renewed enthusiasm for retreatment in both physicians and patients. Unfortunately, the actual increase in SVR with peginterferon combination over rates with standard interferon combination therapy is only 10% to 11%. For these reasons, combination retreatment using peginterferon should probably be limited to the patients in greatest need for therapy and/or those with the greatest likelihood of responding (Table 3). Patients in greatest need of therapy are those with advanced fibrosis or cirrhosis or patients

Table 3. Factors Associated With a Favorable Response During Retreatment

Previous relapse
Partial virological response during the previous treatment
Previous treatment with only interferon monotherapy
HCV genotype 2 or 3
Non-African American race

with symptoms or extrahepatic manifestations of hepatitis C. Patients with the greatest likelihood of a response to retreatment are relapsers or those who had a significant decline (at least 2 log₁₀ units) in serum HCV RNA levels during previous therapy. Response to retreatment is also more likely in non-responders to interferon monotherapy and those infected with HCV genotypes 2 or 3.

Another means of limiting retreatment is to assess patients for an early virological response and discontinue therapy early in patients showing little decrease in HCV RNA levels. In treatment-naïve patients, preliminary data suggest that the likelihood of achieving an SVR is best predicted by an early virological response, a 2 log₁₀ unit decrease in HCV RNA by 12 weeks of therapy.⁶ Among naïve populations, less than 2% of patients who fail to achieve an early virological response ultimately achieve an SVR, and these patients represent less than 1% of all sustained responders. Unfortunately, this same algorithm may not apply to patients undergoing retreatment. In a preliminary study, only 7% of patients who did not have a 2 log₁₀ decrease in HCV RNA during the first 12 weeks of retreatment with peginterferon and ribavirin achieved a sustained response, whereas 41% of patients with a 2 log₁₀ decrease in HCV RNA achieved SVR. Thus, an early virological response may not be as predictive of SVR during retreatment as it is in the treatment-naïve population.

An important reason for relapse and non-response is noncompliance with the prescribed treatment. Noncompliance may be secondary to poor counseling and education regarding side effects and their management by the treating physician, or simply a lack of commitment to treatment by the patient. Retreatment is more likely to be successful if the reasons for noncompliance are corrected. If patients were intolerant of treatment despite adequate management of side effects, retreatment is unlikely to be tolerated and should be avoided.^{15,18}

Options for Patients With Continued Non-Response

As noted above, the number of non-responders who achieve a sustained virological response after retreatment, even with peginterferon and ribavirin, is limited. These patients should be classified into 2 groups, those with

advanced fibrosis or cirrhosis and those with either none or only mild degrees of fibrosis. This later group of patients has an excellent long-term prognosis and is at low risk for development of cirrhosis within the next 5 to 10 years or possibly longer. There is, therefore, no imminent need to retreat these patients, especially if they exhibit characteristics suggestive of continued non-response. Careful observation over several years with retreatment only after more effective therapies are available is an appropriate approach to management of such patients. This approach underscores the importance of performing a liver biopsy and assessing hepatic histology before initial therapy, especially in patients with HCV genotype 1 in whom the likelihood of not achieving an SVR is at least 50%.

Non-responders after retreatment who have advanced fibrosis or cirrhosis are at significant risk for developing cirrhosis and/or hepatic decompensation in the subsequent 5 to 10 years. Continuing low-dose peginterferon as maintenance therapy has been proposed as a possible treatment for these patients. The concept of maintenance therapy is based on the observation that up to 40% of non-responders have a histological response during treatment.^{9,22} A single-center, randomized, controlled trial tested this hypothesis.²³ In this study, non-responders to a 24-week course of interferon monotherapy were randomly assigned to either remain on interferon (3 MU 3 times a week) or stop treatment. After 2.5 years, patients randomized to maintenance interferon therapy had significant reductions in HCV RNA levels, as well as improvements in hepatic inflammation and fibrosis when compared with the pretreatment liver biopsy. In contrast, patients randomized to stop interferon therapy had a return of HCV RNA levels to baseline, no improvements in hepatic inflammation, and progression in liver fibrosis. Importantly, patients included in this study first underwent repeat liver biopsy to ensure that they had achieved a histological response before proceeding with maintenance interferon therapy. Nearly all patients also had a significant decrease in serum HCV RNA levels similar to that shown in Fig. 1. Other studies have shown that histological responses correlate with a decrease in the serum level of HCV RNA during therapy.⁹ These results suggest that maintenance therapy with interferon may lead to continued viral suppression and improvements in necro-inflammatory changes in the liver and prevention of progression of fibrosis. This important hypothesis is the focus of 2 large multicenter, randomized, controlled trials using low doses of peginterferon in patients with advanced fibrosis or cirrhosis due to hepatitis C. Endpoints in these trials are prevention of worsening of fibrosis and prevention of cirrhosis, clinical decompensation, and hepatocel-

lular carcinoma. Until results from these studies are available, use of maintenance interferon therapy should be considered experimental and of unproven benefit.

Summary and Future Research Needs

Since interferon first became available over a decade ago, large numbers of patients with chronic hepatitis C have been treated with either interferon or the combination of interferon and ribavirin. Unfortunately, more than half of these patients remained viremic. The development of peginterferons and their use with ribavirin has created enthusiasm for retreatment of previous non-responders. Unfortunately, sustained responses to retreatment occur in only a limited number of patients. For these reasons, retreatment with peginterferon and ribavirin should be reserved for patients with favorable factors for achieving an SVR. These include patients with prior relapse or a partial virological response, infection with HCV genotypes 2 or 3, and previous therapy with interferon alone.

The decision to retreat a patient should not only be based on the likelihood for response, but also on the severity of the liver disease, which determines the overall risk that the patient may develop cirrhosis or advanced liver disease in the future. This underscores the need to perform a liver biopsy before therapy, especially in patients with HCV genotype 1 who have a significantly lower likelihood for non-response. Patients who remain viremic despite retreatment can be safely observed without continued therapy if their liver disease is mild. Maintenance therapy utilizing low-dose peginterferon is currently being evaluated as a possible way to prevent cirrhosis and decompensation in patients with advanced fibrosis and cirrhosis who fail to have a sustained response to treatment.

The limited benefit of peginterferon and ribavirin in the population of non-responders underscores the need for better treatments for chronic hepatitis C. This is almost certain to be in the form of oral, direct antiviral agents. A better understanding of those host immunologic and genetic factors, which favor non-response, could also provide important insight into the development of more effective therapies for these patients. In the meantime, ongoing studies should clarify the role of maintenance therapy and that subset of non-responders who are most likely to benefit from this approach.

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