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 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.

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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) trial[1] 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 alfa 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 study[4] 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 simply do not receive proper counseling about side-effect management from their physician. A preliminary report[8] 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.

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

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 observation[9] 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 trial[1] 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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