Treatment options for nonresponders and relapsers to initial therapy for hepatitis C

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ABSTRACT

As treatment for chronic hepatitis C virus (HCV) infection has advanced over the past decade, efforts have evolved to retreat patients who did not achieve a sustained virologic response to previous antiviral regimens. Retreating nonresponders to interferon alfa monotherapy with a combination of interferon and ribavirin yields a sustained virologic response in 9% to 32% of patients, whereas retreatment with peginterferon alfa plus ribavirin yields a sustained virologic response in up to 30% to 40% of patients. Sustained virologic response is more likely in retreated patients with HCV genotype 2 or 3, low serum HCV RNA levels, and lack of response to prior interferon monotherapy. Retreatment of nonresponders to interferon–ribavirin combination therapy is associated with lower response rates (≤ 20%). Despite treatment advances, the efficacy of current antiviral regimens for nonresponders remains inadequate. The next few years will see more-targeted antiviral regimens for these patients and therapies focused on slowing the progression of liver disease rather than viral eradication.

Over the past decade, treatments for chronic hepatitis C have evolved from monotherapy with interferon alfa to combinations of pegylated interferon alfa (peginterferon) and ribavirin. As these regimens have evolved, their associated rates of sustained eradication of hepatitis C virus (HCV) have progressed from levels as low as 5% for a 6-month course of interferon monotherapy to 55% with recent regimens of peginterferon plus ribavirin.[1–3]

Despite these gains, many patients remain unresponsive to interferon-based therapy or relapse after therapy ends. Retreatment of these patients, especially those in advanced stages of liver disease, remains an important challenge to investigators and clinicians. This article reviews the specifics of this challenge, the progress that has been made to date, and potential regimens and strategies to combat it in the future.

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CATEGORIES OF RESPONSE TO THERAPY

Any discussion of treatment options for nonresponders to therapy for hepatitis C should begin by defining terms. The 1997 National Institutes of Health Consensus Development Conference clarified the definitions of response patterns to antiviral treatment.[4] It should be emphasized that as treatment for hepatitis C has evolved, so has the sensitivity of assays for viral load (HCV RNA). Current studies use an HCV RNA threshold of 100 copies/mL or 50 IU/mL as the lower limit of viral detection.

End-of-treatment virologic response is defined as an undetectable level of HCV RNA by polymerase chain reaction at the completion of therapy.[3,4] With sensitive polymerase chain reaction assays, **sustained virologic response** is defined as an undetectable HCV RNA level 6 months after therapy is discontinued.

In contrast, **nonresponders** are a heterogeneous group of patients who remain positive for HCV RNA during the course of treatment.[3,4] They may be **true nonresponders**, whose HCV RNA levels are unaffected by treatment, or **partial responders**, who show a significant drop in HCV RNA with treatment but in whom HCV RNA never becomes undetectable.[3–7]

Still other patients achieve HCV RNA levels that are undetectable by sensitive assays during therapy but later become detectable as treatment con-

TABLE 1
Characteristics commonly seen in nonresponders to antiviral therapy for hepatitis C

HCV genotype 1	Male sex
Advanced liver disease (cirrhosis)	African-American race
Serum HCV RNA greater than 2 million copies/mL	Obesity

tinues.[3–8] This **breakthrough** response pattern has an uncertain etiology, but it may result from mutations that render the virus interferon-resistant and contribute to the complexity of HCV quasispecies. This type of response may also result from production of antibodies against interferon.[5–7]

Finally, **relapsers** are patients in whom HCV RNA is undetectable at the end of a full course of therapy but whose viral levels again become detectable when treatment is discontinued. Such relapses have become less frequent with the advent of regimens that use peginterferon and ribavirin for an adequate length of time.[3–8]

Table 1 lists patient characteristics that are frequently associated with inadequate response to antiviral therapy for hepatitis C.

INITIAL ANTIVIRAL THERAPY: WHERE WE STAND TODAY

In 2003, standard therapy for previously untreated patients with chronic hepatitis C consists of a combination of peginterferon and ribavirin. Patients with HCV genotype 1 usually require a full 48-week course of this regimen, whereas those with HCV genotype 2 or 3 may require only 24 weeks of therapy.[3]

Accurate identification of patients unlikely to achieve sustained virologic response relies on a measure known as *early virologic response*, defined as a 2-log drop in HCV RNA after 12 weeks of therapy, or undetectability of HCV RNA after 24 weeks of therapy. Patients who do not achieve an early virologic response are unlikely to respond to a full course of therapy, so this measure can be used to guide decisions to shorten the therapy course for these patients, minimizing potential side effects and costs.

In addition to early virologic response, good adherence to treatment is also associated with sustained virologic response. This is especially true during the first 12 weeks of therapy, which is the most critical period.

ANTIVIRAL TREATMENT OF NONRESPONDERS: OBJECTIVES AND GENERAL OUTCOMES

The primary goal of antiviral therapy has always been to achieve viral eradication. But as treatment of HCV infection has evolved, additional outcomes have gained importance, such as histologic response (improvement of inflammation and fibrosis on liver biopsy) and health-related quality of life. Histologic response is especially important in nonresponders whose disease has already demonstrated resistance to therapy.[8] The main goals of therapy in these patients are to reduce hepatic inflammation, slow progression of fibrosis to cirrhosis, and reduce the risk of hepatic decompensation and hepatocellular carcinoma.[8]

The characteristics of patients considered nonresponders have evolved along with the evolution of treatment regimens. At first, most nonresponders had been treated with standard interferon monotherapy, which eradicated HCV in only 15% to 20% of infected patients, leaving 80% to 85% of patients as nonresponders. As more effective treatment with interferon alfa-2b and ribavirin became widely available, the proportion of nonresponding patients dropped to 50% to 60% of the treated group. The advent of combination therapy with peginterferon and ribavirin has reduced the proportion of nonresponding patients further, but it has left us with a nonresponder population that is potentially more difficult to retreat.

Patients previously treated only with interferon monotherapy stand a good chance of viral eradication with a combination of peginterferon and ribavirin. However, viral eradication through retreatment is more difficult in patients who have not responded to combination therapy with interferon and ribavirin. In general, the decision to retreat a nonresponder should be based on the patient's previous pattern of response, the regimen used, the severity of underlying liver disease, the HCV genotype, and the patient's prior drug tolerance **(Table 2)**.[3]

REGIMENS FOR NONRESPONDERS

Results with interferon-based regimens

Retreatment with interferon-based regimens has generally been studied in nonresponders to interferon monotherapy.[8] One study used a 12-month course of consensus interferon for retreatment of nonresponders and reported sustained virologic

response in 27% of patients who had had breakthroughs during their initial therapy but in only 8% of those who had not had breakthroughs during initial therapy.[9] This suggests that patients with a history of breakthrough are more likely to achieve sustained virologic response with a second course of therapy than are established nonresponders.

Rates of sustained virologic response in retreatment studies using a combination of interferon and ribavirin have ranged from 9% to 32%.[10–13] Some of these studies used weight-based ribavirin dosing (600 to 1,200 mg/day) and varying doses of interferon alfa-2b (3 to 5 MU three times weekly).[12,13] Others have tried induction therapy with daily dosing of interferon, achieving sustained virologic response rates of up to 32%.[10,11] A controlled trial of high-dose induction interferon therapy plus ribavirin versus standard-dose interferon plus ribavirin showed no significant difference in sustained virologic response rates between the two regimens.[11]

Some of these studies were captured in a meta-analysis that included 789 patients from nine clinical trials; all patients had not responded to initial interferon therapy and underwent 6 months of retreatment with interferon and ribavirin.[14] The analysis revealed a sustained virologic response rate of 13.2% and showed that 14 nonresponders to interferon needed to be treated with interferon–ribavirin combination therapy to achieve 1 additional sustained virologic response.

Just as with interferon-naïve patients, HCV genotype remains an important predictor of response in the retreatment of nonresponders.[14–16] The above meta-analysis[14] could not provide information about the potential benefits of longer retreatment therapy (>6 months) in patients with HCV genotype 1.

Results with peginterferon-based regimens

Data currently are limited on outcomes among nonresponders who are retreated with a combination of peginterferon and ribavirin. Preliminary data are available from an ongoing study of 212 nonresponders to interferon monotherapy or interferon–ribavirin combination therapy.[17] Patients were retreated with peginterferon alfa-2a (180 µg/week) plus ribavirin (1,000 to 1,200 mg/day). Those with detectable HCV RNA at week 20 were defined as nonresponders and switched to maintenance therapy with peginterferon alfa-2a, while those without detectable HCV RNA continued a full course of combination therapy for 48 weeks.

An end-of-treatment response was reported in 53% of patients, but a sustained virologic response in only 20%.[17] The rate of sustained virologic response was higher in patients previously treated with interferon monotherapy (34%) than in those previously treated with interferon plus ribavirin (11%). Rates of sustained virologic response also were higher in patients with HCV genotypes other than genotype 1 (60% vs 15%), patients younger than age 50 (25% vs 13%), non-African Americans (22% vs 0%), and patients with at least a 2-log decline in HCV RNA from baseline to treatment week 12 (41% vs 7%).[17]

Similar findings emerged from a retreatment study of 17 nonresponders to prior interferon monotherapy and 84 nonresponders to prior interferon–ribavirin combination therapy.[18] Patients received 1 µg/kg/week of peginterferon alfa-2b plus 1,000 to 1,200 mg/day of ribavirin or 1.5 µg/kg/week of peginterferon alfa-2b plus 800 mg/day of ribavirin. Rates of sustained virologic response were 40% in the first group and 25% in the second group. Among patients who had received prior interferon–ribavirin combination therapy, the sustained virologic response rate was less than 11%.[18]

In a similar study,[19] patients who had relapsed after interferon–ribavirin combination therapy showed end-of-treatment response rates of 71% to 76% after 24 weeks of retreatment with peginterferon plus ribavirin. In comparison, end-of-treatment response rates ranged from 26% to 52% in nonresponders to prior interferon monotherapy or interferon–ribavirin combination therapy.

Preliminary results from a trial of triple therapy with amantadine plus peginterferon alfa-2b and ribavirin suggest a sustained virologic response rate of 19.4% among nonresponders to prior interferon–ribavirin combination therapy.[20]

TABLE 2
Factors to consider before retreating a nonresponding HCV-infected patient

Severity of liver disease	Tolerance of prior therapy
HCV genotype	Prior regimen used
Prior pattern of response to therapy	

■ ALTERNATIVE THERAPIES FOR VIRAL SUPPRESSION

Amantadine, an antiviral agent with activity against influenza A, is a less well-defined treatment option for chronic hepatitis C. Despite early enthusiasm,

amantadine monotherapy has shown little efficacy in patients with HCV infection. Furthermore, adding amantadine to standard interferon seems to confer little additional efficacy against HCV. In two trials in nonresponders to interferon monotherapy, retreatment with interferon plus amantadine yielded a 0% sustained virologic response rate.[21,22]

Amantadine has also been studied as part of a triple-therapy regimen in combination with interferon and ribavirin. This triple regimen has met with mixed results, producing sustained virologic response in 48% of nonresponders to interferon in one study[23] but in less than 20% of nonresponders to interferon and/or to interferon–ribavirin combination therapy in two other studies.[20,24]

STRATEGIES FOR IMPROVING HISTOLOGY IN VIROLOGIC NONRESPONDERS

Maintenance therapy for hepatitis C is based on the premise that long-term interferon therapy may yield histologic improvement. Despite the lack of a virologic response, histologic improvement has been reported in about 40% of nonresponders to interferon-based therapy.[25] Though it does not eradicate the virus, continued interferon therapy may prevent histologic progression to cirrhosis. In one study, nonresponders to interferon monotherapy were randomized to observation or to interferon alfa-2b (3 MU three times weekly) for 2.5 years.[26] Patients receiving therapy showed further declines in HCV RNA titer and some reduction in fibrosis, whereas HCV titers returned to baseline and fibrosis progressed in the observation group.

Several trials are addressing the potential efficacy of maintenance regimens. Patients in the ongoing Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial[17] who remained positive for HCV RNA after 20 weeks of combination therapy with peginterferon alfa-2a and ribavirin were randomized to a weekly maintenance dose of peginterferon alfa-2a alone. The results of this study are expected to show whether long-term maintenance therapy with peginterferon can prevent hepatic fibrosis from progressing and delay complications of advanced liver disease.

Other agents that may help prevent progression of hepatic fibrosis include ursodeoxycholic acid, colchicine, and interferon gamma.

Several clinical trials have shown that ursodeoxycholic acid is associated with a decline in serum alanine aminotransferase levels in HCV-infected patients without a significant impact on serum HCV RNA or improvement of hepatic histology.[27–29]

Colchicine has been used to treat chronic hepatitis C because of its potential antifibrotic effect. However, one trial showed a lower end-of-treatment virologic response rate with the combination of colchicine plus interferon (23%) than with interferon alone (47%), suggesting a lack of antiviral effect for colchicine.[30] Nevertheless, a long-term trial (the Co-Pilot study) randomizing nonresponding patients to a maintenance dose of peginterferon alfa-2b or colchicine is under way.

Interferon gamma seems to have a predominant antifibrotic activity and is being tested in a large multicenter study of patients with HCV infection and advanced fibrosis.

SCREENING FOR AND PREVENTING HEPATOCELLULAR CARCINOMA

The incidence of hepatocellular carcinoma (HCC) in the United States is rising, having climbed from 1.4 per 100,000 population in 1991 to 2.4 per 100,000 population in 1995.[31] This increase continued throughout the 1990s and is attributed mainly to HCV infection.[31] The morbidity, mortality, and economic burden of HCV infection are expected to be substantial over the next decade.[31,32]

Rationale for HCC screening

HCC has a variable natural history. Because tumor size can increase rapidly (median doubling time ranges from 4 to 6 months), screening for HCC with serum alpha fetoprotein monitoring and hepatic ultrasonography has been recommended in HCV-infected patients.[32] Early detection of HCC may lead to improved 5-year survival rates: 60.5% with tumors smaller than 2 cm in diameter, 39.3% with tumors 2 to 5 cm, and 26.8% with tumors larger than 5 cm.[33]

A recent prospective study[34] of 163 HCV-infected patients who were followed for 5 to 7 years with serial ultrasonography and alpha fetoprotein monitoring suggested that the risk for HCC was associated with male sex, age greater than 60, and HCV genotype 1b. Patients with cirrhosis were at the highest risk for HCC, with an annual incidence of 2.5%. While advanced age, male gender, and underlying cirrhosis are known risk factors for HCC, specific HCV genotypes have not been consistently associated with this malignancy. Of the 163 HCV-infected patients in this study, 22 developed HCC over the follow-up period. The tumor was monofocal in 72% of these patients, with a mean diameter of 20.5 mm. Many of the tumors

were amenable to resection, transplantation, or other ablative therapy, including percutaneous ethanol injection and transarterial chemoembolization.

Another study[35] compared the feasibility of surgery between patients infected with HCV or hepatitis B virus who were screened to identify early, subclinical HCC and patients who presented with symptomatic HCC. Significantly more of the screened patients were able to undergo surgery or chemoembolization than were their nonscreened counterparts, and this translated to significantly improved cumulative survival for the screened patients. Although these data require confirmation, this study supports the value of screening programs for HCC in HCV-infected patients.

Antiviral treatment may help prevent HCC

The impact of antiviral therapy on HCC is another important area of research. Interferon therapy has been associated with reduced incidence rates of HCC in HCV-infected patients.

In a retrospective analysis of 2,890 patients with chronic hepatitis C, HCC developed in 3.7% of those who had been treated with interferon compared with 12% of those who had gone untreated.[36] This study also confirmed that patients with advanced fibrosis were at an increased risk of developing HCC. Other retrospective studies have supported this study's findings, showing that 6.7% to 7.6% of interferon-treated patients with chronic hepatitis C developed HCC compared with 12.4% to 13.2% of untreated patients.[37,38]

A recent prospective study of 90 patients with chronic hepatitis C confirmed these results and reported a risk ratio of 0.256 (95% CI, 0.125 to 0.522) for HCC with interferon therapy compared with symptomatic treatment over 8.7 years of follow-up.[39] HCC was diagnosed in 73% of the control patients vs 27% of the interferon-treated patients.

Another prospective study[40] followed patients with hepatitis C for 8 to 11 years after completion of interferon therapy and again found low annual incidence rates of HCC: 0.37% in patients who were complete responders and 0.5% in those who were biochemical responders (ie, patients with sustained normal alanine aminotransferase levels without viral clearance). This compared with an annual incidence of 1.2% in untreated control patients with hepatitis C.

A small trial suggests that postoperative interferon therapy may prevent recurrence of HCC after resection.[41] This study randomized 30 patients with HCV-related HCC to postoperative interferon therapy for 104 weeks or to no therapy. Over a 2-year period following resection, HCC recurred in 12 of 15 patients in the control group compared with 5 of 15 in the treated group. Notably, recurrence of HCC, either from metastases or from new foci (multicentric occurrences), was also less frequent in patients without detectable virus than in those with ongoing viremia.

In addition to these encouraging results with standard interferon, peginterferons are being studied for use as maintenance therapy. Notably, HCC is an important long-term outcome that is being assessed in the ongoing HALT-C trial,[17] discussed above, which is using peginterferon alfa-2a for maintenance therapy.

SUMMARY AND RECOMMENDATIONS

Recommendations for retreatment of nonresponding or relapsing patients with hepatitis C have been frequently revised with the introduction of new therapies over the past decade. Currently, patients who have not responded to interferon monotherapy or interferon-based combination therapy may benefit from a course of peginterferon and ribavirin. However, rates of sustained virologic response in nonresponders to combination therapy with standard interferon and ribavirin generally remain low. The decision to retreat should be based on the patient's stage of liver disease, HCV genotype, and tolerance of previous regimens.

Even after trying all available treatment options, many patients with chronic hepatitis C remain nonresponders. Alternative regimens with antifibrotic agents and maintenance regimens are being considered for these patients, especially for those with significant hepatic fibrosis. Maintenance therapy with peginterferon alone or with alternative therapies may ultimately be shown to prevent progression to cirrhosis and HCC. For now, patients at high risk for HCC should be considered for clinical trials designed to address this issue. These patients also should be considered for screening programs to identify HCC at an early and more treatable stage.

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