

# Clinical Roundtable Monograph

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## Treatment Options for HCV Nonresponders and Relapse Patients

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### Abstract

The current standard-of-care treatment for chronic hepatitis C virus (HCV) infection, peginterferon plus ribavirin, results in a sustained virological response in 39–46% of genotype 1 patients, based on published reports and recently re-affirmed by findings in the IDEAL trial. While several directly targeted oral antiviral medications in development appear promising to decrease genotype 1 treatment failure, these agents are not yet approved for general clinical use, and their contribution to the management of relapsed or refractory HCV patients is uncertain. Other re-treatment approaches may include “watch and wait” or other strategies such as the use of consensus interferon plus ribavirin. Consensus interferon, a wholly synthetic interferon, was developed based on the most commonly represented amino acid sequence of the 14 different subtypes of interferon- $\alpha$  and has been shown in clinical trials to produce sustained virological responses in up to one-third of patients who do not respond to initial therapy and up to 50% of those that relapse after treatment with peginterferon plus ribavirin. In this monograph, the benefits and challenges of each of these available and future treatment options will be discussed with an eye toward optimizing therapy for an individual patient.

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**Target Audience:** This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with relapsed or refractory hepatitis C virus.

**Statement of Need/Program Overview:** Approximately 40–45% of patients with chronic hepatitis C virus (HCV) genotype 1 and 75–80% of those with genotypes 2 and 3 achieve a sustained virologic response (SVR) when treated with the combination of peginterferon alpha and ribavirin for 48 and 24 weeks, respectively. The ability to achieve an SVR during peginterferon alpha and ribavirin treatment is based on 2 separate and independent steps. First, the patient must respond virologically and achieve undetectable HCV RNA (<50 IU/mL). Patients who do not respond virologically cannot achieve an SVR by continuing the same treatment for a longer period of time. Virologic response is primarily dependent on the action of peginterferon alpha and, to a much smaller degree, ribavirin. The second step in achieving an SVR is the prevention of relapse. This is primarily a function of the action of ribavirin and the maintenance of its dosing but is also affected by how quickly the patient achieves undetectable HCV RNA after the initiation of treatment and how long the patient remains on treatment after achieving undetectable HCV RNA. Patients with HCV nonresponse can be classified into 3 patient groups: 1) nonresponse, 2) breakthrough, and 3) relapse. Many patients with previous nonresponse can be retreated successfully and achieve an SVR. Identifying which HCV nonresponders are appropriate candidates for retreatment requires a complete understanding of the various virologic response patterns and the pitfalls associated with achieving and maintaining virologic response.

**Educational Objectives:** After completing this activity, the participant should be better able to:

1. Outline standard definitions of response and nonresponse to hepatitis C virus therapy.
2. Discuss factors associated with nonresponse to hepatitis C virus therapy.
3. Identify criteria that may help to identify nonresponders who are good candidates for retreatment.
4. Summarize data from studies of different retreatment strategies.
5. Describe appropriate virologic goals of therapy for nonresponders undergoing retreatment.

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### Included in EMBASE

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# The Importance of Successful Re-treatment in Refractory HCV Patients

Maria H. Sjogren, MD, MPH, FACP

The standard of care for chronic hepatitis C virus (HCV) has noticeably improved since the approval of interferon therapy more than a decade ago in the United States; however, despite improvements in treatment, many patients still do not respond adequately to initial therapy. Among these patients are nonresponders, who do not achieve viral clearance at established milestones (week 12 or 24 of therapy) as well as relapsers, who do achieve an undetectable level of HCV RNA by the end of treatment but whose serum HCV RNA levels become detectable sometime thereafter. Some patients only partially respond to treatment, experiencing a modest 1–2 log<sub>10</sub> drop in HCV RNA levels. Currently, the overall sustained virological response (SVR) rates associated with either peginterferon alpha-2a or peginterferon alpha-2b and ribavirin are only approximately 55–65% across all genotypes.<sup>1,2</sup>

The importance of a successful re-treatment strategy for refractory or relapsed patients with HCV cannot be overemphasized. There are more than 4 million people in the United States who are actively infected with HCV, and an estimated 8,000–10,000 deaths each year are attributable to complications of chronic hepatitis C.<sup>3</sup> The total medical costs for patients with HCV infections are expected to increase dramatically, from \$30 billion to more than \$85 billion, over the next 20 years.<sup>4</sup> Over the next 2 decades, the number of patients with decompensated liver disease and hepatocellular carcinoma will increase dramatically, raising the need for liver transplantation for these patients.

While patients with advanced, decompensated HCV-related liver disease require liver transplantation to survive, it is not a panacea and it poses a number of challenges. First, the availability of organs is an ongoing problem. In any given year, only about one-third of the people on the national liver transplant waiting list receive one.<sup>5</sup> Second, when a patient with HCV infection does receive a transplant, recurrent infection with HCV post-transplant is almost universal.<sup>6</sup> Post-transplant re-infection is often associated with poor outcomes; for example, it is a significant cause of graft dysfunction and impairs both the patient and graft survival.<sup>7</sup> A classic study by Feray and colleagues of 652 HCV patients who underwent liver transplantation found a 5-year patient survival rate of 72%, and a 10% risk of cirrhosis by year 5.<sup>8</sup>

A third major concern associated with liver transplantation is long-term quality of life. There is a documented reduction in health-related quality of life among HCV patients who experience long-term survival after transplantation. In one study, Feurer and colleagues assessed functional performance, liver function, and HCV recurrence in 75 adult transplant recipients, 28 of whom were infected with HCV.<sup>9</sup> The authors found that functional performance improved through year 2 after transplantation for all patients, but then significantly declined only in those with HCV. Thus, it is clear that liver transplantation, although life saving, is fraught with serious medical consequences and should not be seen as an ideal solution for managing patients who are refractory to standard therapy or who relapse during or after therapy. There is a clear need for the HCV research community to aggressively pursue new therapeutic options for the “difficult to treat” patient.

## Predictive Factors for Treatment Failure With Peginterferon and Ribavirin

What features characterize the “difficult to treat” patient? There are a number of well-documented factors that impact a patient’s likelihood of achieving a SVR with the standard-of-care peginterferon and ribavirin therapy. Viral genotype is a strong determinant of response—SVR rates with peginterferon and ribavirin have been reported to be as high as 88% for patients with genotype 2 or 3 disease; however, only about 40–45% of patients with genotype 1 disease achieve a SVR.<sup>1,2</sup> High viral load is a second predictor of non-response, particularly for genotype 1-infected patients.<sup>10</sup> Metabolic factors, such as increased waist circumference, high body mass index, and glucose metabolic impairment, have also been associated with lack of response.<sup>11</sup>

Advanced age has been documented as a negative predictor of response to peginterferon and ribavirin therapy. Reddy and colleagues examined data from 569 genotype-1 patients enrolled in 2 phase III studies of peginterferon alpha-2a plus ribavirin and found that SVR rates were significantly lower in patients over the age of 50.<sup>12</sup> The patients received peginterferon alpha-2a 180 micrograms per week plus ribavirin 1,000–1,200 mg per day for 48 weeks. The SVR rate was 52% for patients 50 years old or younger, but

was only 39% for patients over the age of 50 ( $P=.0073$ ). Higher relapse rates were seen in the older patient group than were seen in the younger group (41% vs 25%;  $P=.0042$ ). The authors noted that the older patients experienced more adverse events (AEs) and required more dose modifications. This resulted in a lower cumulative peginterferon alpha-2a exposure and significantly lower cumulative ribavirin exposure among the older patients, likely accounting for the difference in SVR and relapse rates.

Another factor that is predictive for a poor response to interferon-based therapy is advanced fibrosis level and cirrhosis. For example, Everson and colleagues examined data from 1,046 patients enrolled in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial.<sup>13</sup> These patients had failed prior treatment with interferon or peginterferon with or without ribavirin, and all had Ishak fibrosis scores of at least 3. In the HALT-C trial, these patients were re-treated with peginterferon alpha-2a and ribavirin. The patients were divided into 4 groups: 1) bridging fibrosis (Ishak 3 and 4) with platelet counts over 125,000/mm<sup>3</sup> (n=559); 2) bridging fibrosis with platelet counts less than or equal to 125,000/mm<sup>3</sup> (n=96); 3) cirrhosis (Ishak 5 and 6) with platelet counts over 125,000/mm<sup>3</sup> (n=198); and 4) cirrhosis with platelet counts less than or equal to 125,000/mm<sup>3</sup> (n=193). The authors found that a significant reduction in SVR rates occurred as disease severity increased, with SVR rates of 23%, 17%, 10%, and 9% in groups 1, 2, 3, and 4, respectively ( $P<.0001$ ). This effect was independent of age, ethnicity, HCV genotype, HCV level, and type of prior therapy.

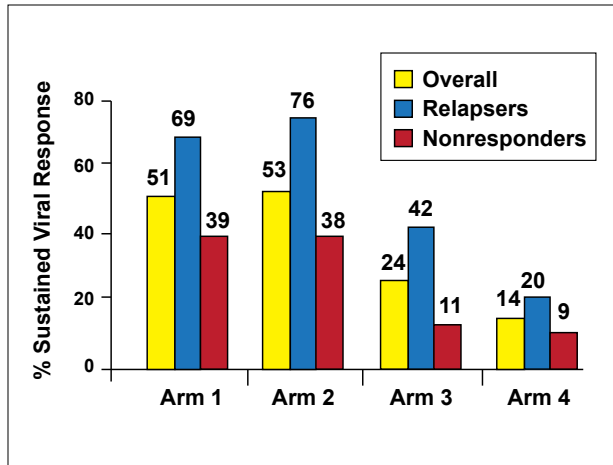
### “Watch and Wait” for Relapsed/Refractory Patients

Because specifically targeted antiviral therapy is not yet approved for HCV, there is a need to critically assess our treatment options for patients who have relapsed or are refractory to treatment with peginterferon and ribavirin. It is not uncommon for a physician to take a “watch and wait” approach, as long as the patient has not progressed to decompensated liver disease. In this approach, no treatment is given, and liver function is monitored over time using a variety of methods, including routine laboratory tests, serum markers of fibrosis and inflammation, liver biopsy, and imaging studies. The hope with the “watch and wait” approach is to buy the patient time during which more effective medications may become approved and available.

There are a number of possible concerns with the “watch and wait” tactic that physicians should keep in mind. One is the ongoing need for liver function monitoring, which can be difficult to accomplish at optimal intervals. If the patient has fibrosis or cirrhosis, this monitoring includes imaging studies, with their associ-

ated inconvenience and cost. In addition, computerized tomography (CT) and magnetic resonance imaging (MRI) studies expose the patient to external radiation, which presents a problem when repeated studies are performed over the course of several years. These imaging studies are also not sensitive enough to precisely measure the amount of hepatic fibrosis or to detect early cirrhosis, so follow-up liver biopsies may become necessary for some patients.<sup>14</sup>

Many relapsed and refractory hepatitis C patients are waiting for new antiviral medications to be developed and approved, and indeed, there are numerous directly targeted oral antivirals in development. One of the furthest along the developmental pipeline is telaprevir, a protease inhibitor that is in phase III trials. Very recent data on the use of telaprevir in relapsed and refractory patient populations were presented by McHutchison and colleagues at the 2009 meeting of the American Association for the Study of Liver Disease (AASLD). The phase II trial (PROVE3) enrolled 453 genotype 1 chronic hepatitis C patients who were non-responders, partial responders, or relapsers following a prior course of peginterferon plus ribavirin.<sup>15</sup> These patients were randomized into 4 arms. The first arm received peginterferon alpha-2a 180 µg weekly, 1,000–1,200 mg of ribavirin daily, and telaprevir 750 mg 3 times daily for 12 weeks. This was then followed by treatment with peginterferon plus ribavirin for an additional 12 weeks. The second arm received peginterferon, ribavirin, and telaprevir for 24 weeks, followed by peginterferon plus ribavirin for 24 weeks. The third arm received peginterferon and telaprevir for 24 weeks. The fourth arm (control) received standard therapy with peginterferon plus ribavirin for 48 weeks. The overall SVR rates in this study were 51%, 53%, 24%, and 14% in arms 1, 2, 3, and 4, respectively. The SVR rates among prior nonresponders were 39%, 38%, 11%, and 9%, respectively; among prior relapsers, rates were 69%, 76%, 42%, and 20%, respectively; and among patients with prior viral breakthrough while on treatment, rates were 57%, 63%, 36%, and 40%, respectively. It should also be noted that the nonresponder group control arm produced higher SVR rates (9%) than those previously reported in other published studies (Figure 1). This possibly suggests that these patients had fewer negative prognostic factors associated with poor response. Factors such as unknown adherence to prior therapy, lack of cirrhosis, and partial responders to first-line treatment all could have contributed to higher response rates seen in the control arm and in the experimental arms. The authors noted that AEs occurred with greater frequency in the telaprevir arms than they did in the standard therapy arm; these included fatigue, nausea, diarrhea, headache, skin rash, pruritus, anemia, insomnia, fever, chills, and hair loss. A rash leading to treatment discontinuation occurred in 4%, 6%, 5%, and 0% of patients in arms 1, 2, 3, and 4, respectively. While these data appear promising, they need to be confirmed in larger, phase III trials.



**Figure 1.** Treatment response rates from the PROVE 3 trial.

Data from McHutchinson J. AASLD Annual Meeting 2009: Abstract 66.

A second protease inhibitor, boceprevir, is also in phase III trials for chronic hepatitis C. Data from the phase II SPRINT-1 study were presented at the 2009 AASLD meeting by Kwo and colleagues.<sup>16</sup> In SPRINT-1, 600 treatment-naïve genotype 1-infected patients were randomized to receive various schedules of boceprevir 800 mg 3 times daily, peginterferon alpha-2b 1.5 µg/kg once weekly, and weight-based ribavirin 800–1,400 mg daily. Kwo presented a data analysis from 206 patients in 2 treatment arms from the study. The first arm received peginterferon plus ribavirin for a 4-week lead-in period, then continued on all 3 medications for an additional 24 weeks. The second arm also had the 4-week lead-in with peginterferon plus ribavirin, followed by an additional 44 weeks of treatment with all 3 medications. Among the 50 patients with less than a 1 log<sub>10</sub> copies/mL HCV RNA reduction in HCV RNA after the 4-week lead-in, the SVR rate was 25% in arm 1 and 55% in arm 2. The SVR rates were higher for patients who had greater reductions in HCV RNA levels after the 4-week lead-in period (Table 1). The most common AEs reported in the boceprevir arms were fatigue, anemia, nausea, and headache.

These data for both telaprevir and boceprevir are encouraging. Certainly more data and more strongly powered studies on the use of these medications for relapsed and refractory patients or for patients with advanced disease would be desirable, particularly for those patients who are currently “watching and waiting.” Phase III trials are now under way for both agents, which will be followed with interest.

Despite the encouraging results from the trials of oral antivirals, there are concerns with these types of medications that should be addressed. First, there is the issue of

**Table 1.** Sustained Virological Response Rates as Broken Down by Week 4 log<sub>10</sub> Copies/mL Hepatitis C Virus RNA Reduction

SVR, n/N (%)	Arm 1: 28 weeks	Arm 2: 48 weeks
Week 4 log <sub>10</sub> copies/mL HCV RNA reduction		
<0.5	2/7 (29)	4/9 (44)
0.5 – <1.0	5/21 (24)	8/13 (62)
1.0 – <1.5	3/10 (30)	11/17 (65)
1.5 – <2.0	8/11 (73)	8/10 (80)
2.0 – <3.0	14/21 (67)	11/14 (79)
3.0 – <4.0	10/12 (83)	14/17 (82)
≥4.0	11/11 (100)	11/12 (92)
Undetectable	3/3 (100)	9/9 (100)

Data from Kwo PY. AASLD Annual Meeting 2009: Abstract 62.

the development of resistance to oral antiviral medications. Although much needs to be learned about viral resistance to protease or polymerase inhibitors, we know that viral resistance occurs when these medications are unable to cease HCV replication. When new HCV viral copies are made, genetic changes (single, double, triple mutations) occur, allowing HCV to efficiently replicate despite the continuous administration of the polymerase or protease inhibitors. Treatment of viral resistant mutants will be a challenge and most likely will require the development of newer drugs.

A second concern is compliance with an every-8-hour dosing schedule and certain food restrictions. These medications are given in conjunction with peginterferon and ribavirin, bringing forth the question of “real-world” medication adherence. One of the most important factors affecting patient adherence to their medication is the prescribed number of doses per day. Indeed, a large meta-analysis of 76 studies conducted by Claxton and colleagues found that mean dose-taking compliance for 1-dose daily regimens was 79% +/- 14%; for 2-dose daily regimens was 69% +/- 15%; for 3-dose daily regimens was 65% +/- 16%, and for 4-dose daily regimens was 51% +/- 20% (*P*<.001 for 1 vs. 3 doses, 1 vs 4 doses, and 2 vs 4 doses).<sup>17</sup> Therefore, we can assume that in actual clinical practice, only about two-thirds of patients will actually take their oral antiviral medication as prescribed 3 times per day. There are some open-label data for telaprevir indicating that a 2-times daily dosing schedule may be as effective as a 3-times daily schedule<sup>18</sup>; still, the data from Claxton and colleagues indicate that the difference between dosing 2 or 3 times per day is not statistically significant in terms of mean adherence rate.

The consequences of nonadherence to oral medications have been well-documented for a variety of diseases. Poor adherence and persistence can severely impede the efficacy of oral regimens.<sup>19</sup> If a physician is not aware that a patient is not taking an oral therapy as prescribed, he or she may attribute progression of the disease to a lack of activity of the drug, and therefore may unnecessarily change a regimen.<sup>20</sup> The toxicities of a drug may be increased, especially if a patient is taking doses too close together or at the wrong time of day. Lastly, nonadherence has been associated with an increased consumption of healthcare resources, including more physician visits, higher hospitalization rates, and longer stays.<sup>21-23</sup>

In summary, there is a growing pool of patients with compensated liver disease who have relapsed or are refractory to treatment with peginterferon and ribavirin. Many patients are simply “watching and waiting” for newer targeted agents to become approved, only to have their disease progress to the point of needing a liver transplant. Thus, these patients represent a strong unmet need in the HCV treatment community, and alternative treatment options need to be discussed.

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# Optimizing Re-treatment Approaches in Relapsing and Other Nonresponding HCV Patients

Brian L. Pearlman, MD, FACP

In this section, we will look at currently available options for re-treating relapsing and other nonresponding HCV patients. Before discussing these options, it is important to carefully define the various types of response over time to peginterferon and ribavirin therapy. The first is the rapid virologic response (RVR), which is defined as undetectable serum HCV RNA levels with a sensitive nucleic acid assay, after 4 weeks of therapy. The second is the early virologic response (EVR). EVR can be broken down into 2 subgroups. The first are those patients who have at least a 2- $\log_{10}$  drop in HCV RNA after 12 weeks of treatment but still have detectable viremia. These patients achieve what is called a partial EVR. The second subgroup are patients who have completely undetectable HCV RNA levels after 12 weeks of treatment; these achieve a complete EVR. Another useful term is the end-of-treatment response (EOTR), which is defined as undetectable HCV RNA levels at the end of the treatment interval, however long it may be. Finally, the gold standard of viral elimination is the sustained virologic response (SVR), which is undetectable serum HCV RNA levels 24 weeks after the end of treatment. In a given cohort of treatment-naïve patients treated with peginterferon and ribavirin, approximately 15% of the total will achieve an RVR; 35% of the total will have a complete EVR, and 20% will have a null-response, defined as less than a 2- $\log_{10}$  viral drop at 12 weeks of therapy.

The above response categories are quite useful for predicting the likelihood of an eventual SVR. For example, Jensen and colleagues conducted a retrospective study of 729 HCV patients treated with peginterferon alpha-2a and weight-based ribavirin (1,000–1,200 mg/day), and they discovered that the SVR rate was 89% among patients with an RVR but only 19% among patients without an RVR.<sup>1</sup> The EVR milestone also carries strong predictive value for a SVR. The first study to document this was by Davis and colleagues in 2003, who found that patients who experienced a complete EVR on treatment with peginterferon alpha-2b and ribavirin went on to have a SVR rate of 84%, compared with only 22% for patients who achieved a partial EVR.<sup>2</sup> Patients who did not reach a 2- $\log_{10}$  drop in viral load from baseline, or null-responders, however, did not respond to a further 36 weeks of peginterferon (a 0% chance of achieving SVR). Thus, the EVR has been shown to have excellent negative predictive value for treatment failure, such that treatment is now generally discontinued for patients who fail to achieve at least a partial EVR.

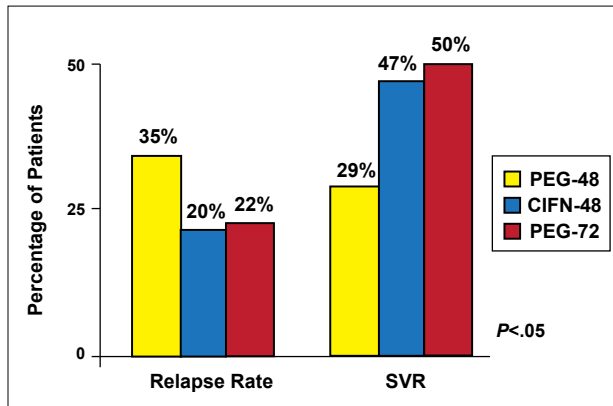
Some data have demonstrated that the SVR rate for patients who achieve a partial EVR can be improved with a longer treatment duration. Pearlman and colleagues conducted a prospective trial in which patients who achieved a partial EVR and subsequent undetectable viremia at 24 weeks (deemed slow responders) on therapy with peginterferon alpha-2b and 800–1,400 mg/day of ribavirin were randomized to complete a total of 48 or 72 weeks of therapy.<sup>3</sup> Although there was no difference in EOTR between the 2 groups, the SVR rates were significantly higher with extended treatment (38% vs 18%;  $P=.026$ ). Treatment extension is not universally accepted, however. In a study from 11 centers in Italy, Mangia and colleagues tried an individualized treatment strategy based on time to viral negativity on therapy. In a subset of study patients who had achieved partial EVR and viral negativity at 24 weeks, those randomized to extended therapy of 72 weeks had no statistically improved rate in SVR compared to those given standard duration therapy (48 weeks; 7.5% vs 0%;  $P=NS$ ). Actually, extended treatment duration engendered a higher rate of voluntary therapy withdrawal relative to the shorter therapy arm.

## Re-treatment for Relapsing and Other Nonresponding Patients With HCV

As opposed to other nonresponding patients, the relapser has undetectable HCV RNA at the end of treatment, but develops detectable viremia by week 24 post-treatment. Although the relapse rate is low for patients with genotype 2 or 3 infection, the relapse rate is approximately 30% for patients infected with genotype 1 HCV.<sup>4</sup> In addition, there are some patients who experience viral breakthrough. These patients have undetectable viremia at some point during treatment, but experience an on-treatment viral breakthrough. Viral breakthrough is usually due to poor adherence.

Is re-treating the relapsed patient with peginterferon and ribavirin a good option? In 2009, Poynard and colleagues published a study showing that re-treatment of relapsed patients with peginterferon plus ribavirin produces a SVR in about one-third of patients.<sup>5</sup> In their prospective open-label study, 2,333 chronic HCV-infected patients with significant fibrosis/cirrhosis whose previous interferon alpha or peginterferon alpha plus ribavirin therapy had either failed or who had relapsed after treatment were re-treated with peginterferon alpha-2b 1.5  $\mu\text{g}/\text{kg}/\text{week}$  plus weight-





**Figure 2.** Rates of virologic response and relapse. There were no significant differences in SVR between the 48 week CIFN and the 72 week PEG group.

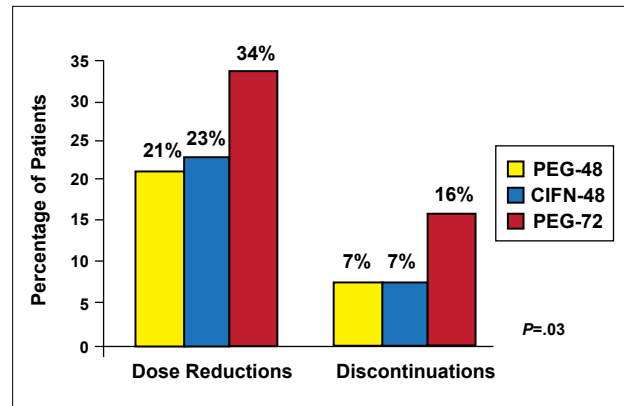
CIFN=consensus interferon; PEG=peginterferon alpha-2b; SVR=sustained virologic response

Data from Pearlman BL, Ehleben C. 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2009). Abstract 815.

based ribavirin 800–1,400 mg per day for 48 weeks. They found that the SVR rate for relapsers was 38%, but was only 14% for nonresponders, regardless of previous treatment type (interferon or peginterferon). For genotype-1–infected patients who relapsed on prior therapy, only 23% achieved a SVR with re-treatment.

Another option that is supported by clinical studies is treatment of relapsers with consensus interferon (CIFN).<sup>6</sup> The consensus interferon molecule has been found to bind to the interferon- $\alpha$  receptor with the highest affinity of all the known interferon- $\alpha$  molecules, including the variants, the recombinants, and the natural subtypes. It appears approximately 5- to 20-fold more active in vitro than any other interferon.<sup>7</sup>

Recent data from our group have supported the roles of CIFN treatment of the relapsed HCV patient.<sup>8</sup> In this study, we compared treating HCV genotype 1-infected patients who had relapsed to peginterferon alpha-2a and ribavirin with consensus interferon plus ribavirin versus re-treating with peginterferon plus ribavirin with standard or extended duration therapy. In the interim analysis, a total of 76 genotype 1-infected patients had been randomized to 3 arms as follows: 1) peginterferon alpha-2b 1.5  $\mu$ g/kg/week plus weight-dosed ribavirin 800–1,400 mg daily for 48 weeks ( $n=14$ ); 2) peginterferon alpha-2b plus ribavirin for 72 weeks ( $n=32$ ; same dose as in arm 1); 3) CIFN 15  $\mu$ g/day plus ribavirin for 48 weeks ( $n=30$ ). The patient population was from an urban center and was somewhat difficult to treat. The SVRs achieved were 29%, 50%, and 47% in arms 1, 2, and 3, respectively ( $P=.02$  for arm 1 vs arm 2 and for arm 1 vs arm 3;  $P=NS$  for arm 2 vs arm 3; Figure 2). Dose reductions were required for 21%, 34%, and 23% of patients in arms 1, 2, and 3, respectively. Discontinuations were seen in 7% in each of the 48-week arms, and in 16% of patients in the 72-week



**Figure 3.** Dose reductions and treatment discontinuations for adverse events or laboratory abnormalities were similar between the 48-weeks treatment groups, but were significantly higher in the 72-weeks arm.

Data from Pearlman BL, Ehleben C. 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2009). Abstract 815.

peginterferon arm (Figure 3). It should be noted that these are preliminary data, and at least 90 patients are expected to be studied in the final analysis.

Data from another recent trial, the DIRECT trial, also support a role for CIFN in the treatment of nonresponder patients.<sup>9</sup> In this multicenter study, 487 patients who had failed treatment with peginterferon plus ribavirin were randomized to receive CIFN at a dose of either 9  $\mu$ g daily or 15 micrograms daily; all patients received ribavirin 1,000–1,200 mg daily. Within these 2 groups of patients, 58–62% had documented advanced fibrosis at baseline liver biopsy (stage F3 or F4), and 80% had been null-responders to previous therapy. Overall SVR rates were 6.9% in the 9  $\mu$ g group and 10.7% in the 15  $\mu$ g group. However, in the subgroup analysis, patients who had a lower baseline fibrosis score (F0–F3) coupled with at least a 2- $\log_{10}$  decrease in HCV RNA in response to previous peginterferon plus ribavirin treatment had higher SVR rates. The SVR rate was 31.6% in the 15  $\mu$ g group. Further analysis of patients who achieve a complete EVR after 12 weeks of CIFN-based therapy, showed that 63.6–81% of these patients ultimately achieve a SVR.

### Selecting Candidates for Re-treatment

When selecting a candidate for re-treatment with peginterferon and ribavirin, it is important to determine if the patient failed the first round of therapy because of adherence problems. One example is the patient who did not take the first round of treatment seriously. A second example might be the patient who took treatment seriously but was going through a major life change, such as unemployment, divorce, or death of a loved one, during the first round of treatment. Perhaps the patient was not adherent at the time, but circumstances have improved to the point at which the patient feels

he or she can now take their medications as prescribed. This type of patient would be a good candidate for re-treatment with peginterferon plus ribavirin, assuming that there were no complicating AEs during the first treatment round.

This brings up an important point about screening for depression before starting therapy with peginterferon, which has known effects upon mood. At our clinic, we screen with validated depression inventories before starting treatment, and we discourage any patients with depression from starting HCV treatment until their depression has been treated. It is important to point out that, in my experience, it is not so much the patients who have a history of depression, even a history of severe depression, who do poorly on peginterferon treatment. It is the patients who have some degree of anxiety or depression at baseline or at the start of treatment that really struggle through therapy.

It is also critical to determine if the refractory/relapsed patient actually took the prescribed dose of ribavirin, or even if dose reductions were initiated on the part of the physician. A very recent study by Hiramitsu and colleagues showed that even small reductions in ribavirin dosing have a dramatic effect upon relapse rates among patients treated with peginterferon plus ribavirin.<sup>10</sup> In their study, 984 patients with genotype 1 disease were treated with peginterferon alpha-2b (60–150 µg/kg weekly according to body weight) plus ribavirin (600–1,000 mg twice daily according to body weight). Dose reductions and discontinuations were allowed, and patients' drug exposure to each medication was calculated by averaging the doses actually taken. For the 472 patients who were HCV RNA negative at week 24 and week 48, the authors found that a 200-mg stepwise reduction in the ribavirin dose was inversely associated with a stepwise increase in the relapse rate from 11% to 60%. Of note, only a 4% relapse rate was found among patients who achieved a complete EVR and who received at least 12 mg/kg/day of ribavirin, even among those whose peginterferon dose was reduced to as little as 0.6 µg/kg/week after week 12. Yet, patients who achieved complete EVR who received less than 12 mg/kg/day of ribavirin had a relapse rate of at least 15%. The authors concluded that maintaining as high a ribavirin dose as possible during the full treatment period can dramatically reduce relapse rates among genotype 1-infected patients treated with peginterferon and ribavirin. In light of these data, physicians and patients may want to explore every option for maintaining high levels of ribavirin exposure during treatment, including aggressive management of AEs as well as ensuring excellent adherence to dosing schedules. In the ADHERE registry, patients at 12 weeks of therapy had achieved statistically significant better adherence using Ribapack compared to generic ribavirin (86.4% vs 77.7%, respectively;  $P=.01$ ).

In short, relapsed patients who may not have received the full course of treatment during the first try for various reasons make excellent candidates for re-treatment. Indeed, the re-treatment of relapsed patients who were adherent in the first

round with a second round of peginterferon plus ribavirin is effective in up to half of patients when an extended 72-week regimen is used, as discussed above.<sup>8</sup> Similarly, nearly half of relapsing patients may see a SVR when re-treated with 48 weeks 15 µg daily CIFN and weight-based ribavirin. Non-responders may also be good candidates for treatment with 15 µg CIFN, as indicated by the 31% SVR rate seen in the DIRECT trial<sup>9</sup> among patients who had a partial response with previous treatment of pegylated interferon and ribavirin.<sup>8</sup>

What about the situation of a poor virologic response despite good adherence? An example of this is the "early null responder" who is characterized by a less-than-1 log<sub>10</sub>-drop in HCV RNA levels at week 4. According to data from the IDEAL study, early null responders have less than a 5% chance of achieving a SVR, regardless of whether they are treated with peginterferon alpha-2a or alpha-2b.<sup>11</sup> Similarly, Reau and colleagues<sup>12</sup> presented retrospective data at the 2008 American Association for the Study of Liver Disease meeting, showing that genotype 1 early null responders had a SVR rate of 3% in their study. This raises the question: Is it worth the cost and side effects of therapy to continue treating, beyond 4 weeks, if the patients have only a 3–5% chance of success? This is a controversial topic that clinicians need to consider on a case-by-case basis.

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## Treatment Options for HCV Nonresponders and Relapse Patients

**CME Post-Test:** Circle the correct answer for each question below.

- The study by Feray and colleagues of 652 HCV patients who underwent liver transplantation found a 5-year patient survival rate of \_\_%, and a \_\_% risk of cirrhosis by year 5.
  - 72%, 10%
  - 72%, 20%
  - 65%, 10%
  - 55%, 20%
- Which of the following factors are associated with a decreased likelihood of achieving a SVR with the standard-of-care peginterferon and ribavirin therapy?
  - HCV genotype 1 infection
  - age over 50
  - high body mass index
  - all of the above
- TRUE OR FALSE? Computerized tomography (CT) and magnetic resonance imaging (MRI) studies alone are sensitive enough to detect early cirrhosis when used as part of a “watch and wait” approach.
  - True
  - False
- In the PROVE3 trial of telaprevir, genotype 1 HCV patients who were non-relapsing non-responders following a prior course of interferon plus ribavirin achieved a SVR rate of \_\_% after triple therapy with peginterferon, ribavirin, and telaprevir for 12 weeks followed by treatment with peginterferon plus ribavirin for an additional 12 weeks.
  - 76%
  - 39%
  - 42%
  - 20%
- In the SPRINT-1 study of boceprevir, the patient population was:
  - genotype 1, treatment-naïve
  - genotype 1, 2, and 3, treatment-naïve
  - genotype 1, relapsers after prior treatment with peginterferon/ribavirin
  - genotype 1, refractory to prior treatment with peginterferon/ribavirin
- According to the study by Claxton and colleagues about medication adherence, which of the following comparisons in mean dose-taking compliance WAS NOT statistically significantly different?
  - 1 dose daily vs 3 doses daily
  - 1 dose daily vs 4 doses daily
  - 2 doses daily vs 3 doses daily
  - 2 doses daily vs 4 doses daily
- In the study by Poynard and colleagues in which 2,333 refractory/relapsed HCV patients with significant fibrosis/cirrhosis were re-treated with peginterferon plus ribavirin, what was the SVR rate for relapsers?
  - 14%
  - 22%
  - 31%
  - 38%
- In the study by Pearlman and colleagues that tested the role of consensus interferon (CIFN) to treat genotype 1 relapsed HCV patients, what was the SVR rate among the 30 patients treated with CIFN for 48 weeks?
  - 29%
  - 34%
  - 47%
  - 50%
- Which of the following HCV patients is NOT a good candidate for re-treatment?
  - a relapsed patient who was not adherent during the first round of treatment
  - a patient with a history of depression who is currently on an anti-depressant
  - a patient who failed peginterferon/ribavirin treatment but did not receive the optimal dose of ribavirin
  - an “early null responder” to peginterferon/ribavirin treatment
- According to the IDEAL study, early null responders on-treatment with peginterferon plus ribavirin have a \_\_% chance of achieving a SVR.
  - less than 5%
  - 10%
  - 18%
  - 22%

# Evaluation Form Treatment Options for HCV Nonresponders and Relapse Patients

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

**Please rate your level of agreement by circling the appropriate rating:**

1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree

**Learning Objectives**

After participating in this activity, I am now better able to:

- |   |   |   |   |   |   |
|---|---|---|---|---|---|
| 1. Outline standard definitions of response and nonresponse to hepatitis C virus therapy.             | 1 | 2 | 3 | 4 | 5 |
| 2. Discuss factors associated with nonresponse to hepatitis C virus therapy.                          | 1 | 2 | 3 | 4 | 5 |
| 3. Identify criteria that may help to identify nonresponders who are good candidates for retreatment. | 1 | 2 | 3 | 4 | 5 |
| 4. Summarize data from studies of different retreatment strategies.                                   | 1 | 2 | 3 | 4 | 5 |
| 5. Describe appropriate virologic goals of therapy for nonresponders undergoing retreatment.          | 1 | 2 | 3 | 4 | 5 |

**Based upon your participation in this activity, choose the statement(s) that apply:**

- I gained new strategies/skills/information that I can apply to my area of practice.
- I plan to implement new strategies/skills/information into my practice.

**What strategies/changes do you plan to implement into your practice?** \_\_\_\_\_

**What barriers do you see to making a change in your practice?** \_\_\_\_\_

**Which of the following best describes the impact of this activity on your performance?**

- I will implement the information in my area of practice.
- I need more information before I can change my practice behavior.
- This activity will not change my practice, as my current practice is consistent with the information presented.
- This activity will not change my practice, as I do not agree with the information presented.

**Please rate your level of agreement by circling the appropriate rating:**

1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree

**The content presented:**

- |   |   |   |   |   |   |
|---|---|---|---|---|---|
| Enhanced my current knowledge base              | 1 | 2 | 3 | 4 | 5 |
| Addressed my most pressing questions            | 1 | 2 | 3 | 4 | 5 |
| Promoted improvements or quality in health care | 1 | 2 | 3 | 4 | 5 |
| Was scientifically rigorous and evidence-based  | 1 | 2 | 3 | 4 | 5 |
| Avoided commercial bias or influence            | 1 | 2 | 3 | 4 | 5 |

**Would you be willing to participate in a post-activity follow-up survey?**    Yes    No

**Please list any topics you would like to see addressed in future educational activities:** \_\_\_\_\_

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

**Post-test Answer Key**

<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>

**Request for Credit**

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**For Physicians Only:** I certify my actual time spent to complete this educational activity to be: \_\_\_\_\_

- I participated in the entire activity and claim 1.0 credits.
- I participated in only part of the activity and claim \_\_\_\_\_ credits.