

a series of articles  
written by medical  
professionals  
about the manage-  
ment and treat-  
ment of hepatitis C

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## Management of Hepatitis C Treatment Failure

Despite impressive progress in the management of chronic hepatitis C over the past ten years, treatment failure still occurs in about half of patients who use current therapies. Sustained virological response (SVR), defined by convention as continued undetectable serum HCV RNA six months after the completion of treatment, occurs in only a limited number of patients undergoing retreatment after failure of initial therapy. This article will discuss the different types of hepatitis C treatment failure, which patients are likely to respond to retreatment, expected SVR rates with retreatment, and management strategies and experimental approaches for patients who have experienced prior treatment failure and are not candidates for retreatment.

### Treatment for Chronic HCV

Treatment of chronic hepatitis C with interferon-based therapy has evolved dramatically since the early 1990s (see **Table 1** for a comparison of treatment response rates). In 1998, the Food and Drug Administration (FDA) approved the combination of interferon alfa-2b plus ribavirin, which became the standard therapy for people with chronic

hepatitis C virus (HCV) infection. Interferon alfa-2b (3 million units [MU] three times weekly) plus ribavirin (1,000-1,200 mg daily) produced SVR rates of 38% and 43%, respectively, in pivotal American and European trials. These studies also showed that patients with HCV genotypes 2 or 3 were more likely to respond to treatment than those with genotype 1 (SVR of 66% vs 29%). Patients with genotype 1 had an increased SVR rate after 48 weeks of therapy (compared with 24 weeks), while those with genotypes 2 or 3 did not see an additional benefit from longer treatment.

Today, the current treatment of choice for chronic hepatitis C is peginterferon (the correct generic name, but also commonly called pegylated interferon)—an altered form of interferon that lasts longer in the body and can be injected once rather than three times weekly—plus daily ribavirin. Schering's peginterferon alfa-2b (Peg-Intron) was approved in January 2001, and Roche's peginterferon alfa-2a (Pegasys) was approved in October 2002. Initial studies showed that peginterferon monotherapy was more than twice as effective as standard interferon monotherapy (SVR of 39% vs 19% with Pegasys vs Roferon-A,

and 23-25% vs 12% with Peg-Intron vs Intron A). Subsequent studies showed that combination therapy with peginterferon plus ribavirin produces an overall SVR rate of 54-61%.

### Treatment Failure

Despite improvements in treatment, many patients still do not respond to initial therapy for chronic hepatitis C.<sup>1</sup> These include relapsers, who experience reappearance of serum HCV RNA after achieving an undetectable level at the conclusion of a course of therapy (an end-of-treatment response), and nonresponders, who do not achieve viral clearance by the completion of therapy. Some patients experience breakthrough nonresponse, an increase in HCV RNA after achieving an undetectable viral load during continuous treatment. Some have no decrease in HCV viral load during therapy, or experience only a modest decrease of 1-2 logs. Others have an HCV RNA decrease of at least 2 logs, but their viral load remains detectable during therapy (often called a partial response). Patients who experience a significant decrease in HCV RNA may demonstrate decreased serum liver enzyme, e.g., alanine aminotransferase (ALT) levels and reduced liver tissue

damage, even if they do not achieve an undetectable viral load.

## Retreatment

Improvements in HCV therapy raise the possibility that people for whom earlier attempts at treatment have failed might be helped by new and better regimens. Approaches to retreatment include use of higher doses of interferon, longer duration of therapy, use of different types of interferon, e.g., peginterferon, and the addition of ribavirin or use of a higher dose. Several factors predict whether retreatment is likely to be successful (see **Table 2**). People who have relapsed are more likely to be successfully retreated than nonresponders, as are those nonresponders who had a significant decrease in HCV RNA during initial treatment (even if they did not achieve an undetectable viral load).

The type of initial treatment also plays an important role. Retreatment with the same regimen is unlikely to be beneficial unless the previous dose and/or duration of therapy were inadequate. Relapse or nonresponse may have been due to noncompliance with a prescribed regimen; if this was the case, better patient education and management of side effects may increase the likelihood of adherence and successful treatment. People who previously experienced treatment failure with a less effective regimen may respond to retreatment with more effective therapy. Patients who received prior treatment with interferon monotherapy are considerably more likely to respond to further treatment than those previously treated with standard or pegylated interferon plus ribavirin.

Other factors that predict the likelihood of successful retreatment

<b>TABLE 1</b>				
<b>Comparison: Sustained Virological Response Rates in Treatment-Naive Patients</b>				
<b>Treatment Regimen</b>	<b>Duration</b>	<b>Sustained Virological Response</b>		
		<b>Overall</b>	<b>Genotype 1</b>	<b>Genotypes 2 or 3</b>
IFN <sup>1</sup>	24 wk	5-10%	2-5%	15-20%
IFN <sup>1</sup>	48 wk	~15%	~10%	~30%
IFN + RBV <sup>2,3</sup>	48 wk	41%	29%	66%
PEG-IFN alfa-2b + RBV <sup>4</sup>	48 wk	54%	42%	82%
PEG-IFN alfa-2b + RBV <sup>5</sup>	48 wk	61%	48%	88%
PEG-IFN alfa-2a + RBV <sup>6</sup>	48 wk	56%	46%	76%
PEG-IFN alfa-2a + RBV <sup>7</sup>	48 wk	61%	51%	78%

*IFN = interferon alfa-2b monotherapy twice weekly; IFN+RBV = interferon alfa-2b twice weekly plus ribavirin 1000-1200 mg daily; PEG-IFN+RBV = peginterferon alfa-2b (Peg-Intron) or alfa-2a (Pegasys) once weekly plus ribavirin 800 mg daily to 1000-1200 mg daily.*

<sup>1</sup>Poynard, T. et al. *Hepatology* 1996, 24:778  
<sup>2</sup>McHutchison, J. et al. *New England Journal of Medicine* 1998, 339:1488  
<sup>3</sup>Poynard, T. et al. *Lancet* 1998, 352:1426  
<sup>4</sup>Manns, M. et al. *Lancet* 2001, 120:958  
<sup>5</sup>Manns, M. et al. *Lancet* 2001, 120:958; with weight-based ribavirin dosing at > 10.6 mg/kg ribavirin by secondary analysis of the study  
<sup>6</sup>Fried, M. et al. *New England Journal of Medicine* 2002, 347:975  
<sup>7</sup>Hadziyannis, S. et al. *Journal of Hepatology* 2002, suppl. 1:3

include lower HCV viral load and infection with HCV genotypes 2 or 3.

## Retreatment of Relapsers

Patients who relapse after initial HCV therapy are more likely to be successfully retreated than initial nonresponders. The combination of interferon plus ribavirin was originally approved by the FDA for retreatment of patients with chronic hepatitis C who had relapsed after treatment with interferon monotherapy. In a large multicenter study by G.L. Davis and colleagues, 48% of relapsed patients treated again with interferon monotherapy achieved an undetectable viral load during treatment, but the sustained response rate was only 5%.<sup>2</sup> In contrast, 82% of initial relapsers retreated with a combination of standard interferon plus ribavirin became HCV RNA negative, and

<b>TABLE 2.</b>	
<b>Factors Influencing Success of Retreatment</b>	
<b>Previous type of response</b>	
Relapse	
Nonresponse	
	Viral breakthrough
	No or <1-2 log decrease in HCV RNA
	≥2 log decrease in HCV RNA
<b>Effectiveness of previous therapy versus effectiveness of retreatment regimen</b>	
<b>Liver disease severity</b>	
<b>HCV genotype</b>	
<b>Tolerance of previous therapy</b>	
<b>Adherence to previous therapy</b>	

47% achieved an SVR.

To date, there has only been one published preliminary study on the use of peginterferon plus ribavirin for retreatment of patients who relapsed after initial treatment with standard interferon plus ribavirin.<sup>3</sup> In this study,

55 patients were retreated with either peginterferon alfa-2b 1.0 µg/kg once weekly plus ribavirin 1000-1200 mg daily or peginterferon alfa-2b 1.5 µg/kg once weekly plus ribavirin 800 mg daily; 32% and 50%, respectively, achieved a SVR.

## Retreatment of Nonresponders

Most published information about retreatment is from studies of standard interferon plus ribavirin in patients who failed previous treatment with interferon monotherapy. S.J. Cheng and colleagues performed a meta-analysis of nine randomized controlled trials (RCTs) comprising 789 patients.<sup>4</sup> After six months of standard combination therapy, the pooled SVR was 13%; combination therapy was almost five times more effective than interferon monotherapy. A second meta-analysis by K.J. Cummings and colleagues looked at 12 RCTs with 941 patients.<sup>5</sup> In this analysis, the pooled SVR was 14% for patients retreated with combination therapy, compared to 2% for those retreated with interferon alone. R. San Miguel and colleagues analyzed ten RCTs with 1728 patients, and found a pooled SVR of 13%.<sup>6</sup> In addition, a systematic review of randomized trials of interferon (with or without ribavirin) showed that ap-

**TABLE 3**

### SVR Rates Following Retreatment According to Prior Therapy

Prior therapy nonresponders	Retreatment regimen	SVR
Interferon monotherapy	Interferon + ribavirin	13-15%
Interferon monotherapy	Peginterferon + ribavirin	25-40%
Interferon + ribavirin	Peginterferon + ribavirin	~10%
Relapsers		
Interferon monotherapy	Interferon + ribavirin	47%
Interferon + ribavirin	Peginterferon + ribavirin	32-50%

*Modified from Shiffman, M.L. Retreatment of patients with chronic hepatitis C. Hepatology 2002, 36(suppl. 1):S128.*

ribavirin in patients who did not respond to standard interferon monotherapy. The rationale for using higher induction dosing comes from studies such as that of A.U. Neumann and colleagues, who showed a more rapid decline in HCV viral load with 10 MU versus 5 MU of interferon daily over 14 days.<sup>7</sup> Furthermore, recent research shows that early viral kinetics correlate with SVR rates in previously untreated patients receiving high-dose induction inter-

feron followed by 5 MU daily for 74 days, then 5 MU three times weekly for 24 weeks; the second group received the same interferon regimen plus ribavirin starting at day 11. One-third (33%) of the patients receiving induction interferon plus ribavirin achieved a SVR, compared with none of those receiving induction interferon alone.

Because it is so new, there are few published studies on the use of peginterferon plus ribavirin

received a typical peginterferon dose (0.5 µg/kg).<sup>9</sup> I. Jacobson and colleagues are conducting a study of peginterferon alfa-2b plus ribavirin in patients with genotype 1 HCV who did not respond to prior treatment with interferon monotherapy or interferon plus ribavirin.<sup>2</sup> Preliminary data from this study show that 16% of patients with genotype 1 who had failed prior interferon monotherapy and were treated with peginterferon 1.5 mg/kg weekly plus ribavirin 800 mg daily achieved a SVR, compared with 27% of patients treated with pegylated interferon 1.0 mg/kg weekly plus ribavirin 1000-1200 mg daily. However, among the patients who did not respond to previous combination therapy with standard interferon plus ribavirin, the SVR rates with retreatment were only 5-9% with the two treatment schedules. Similarly, M. Shiffman of the HALT-C Trial Investigators team has reported preliminary data from a large study of peginterferon alfa-2a 180 mg weekly plus ribavirin 1000-1200 mg daily in patients who did not respond to standard interferon therapy with or without ribavirin.<sup>9</sup> Patients who previously received interferon monotherapy had a SVR rate of 34%, compared with a SVR rate of 11% for those who initially had received standard interferon plus ribavirin.

## Management Options for Nonresponders

In summary, 47% of patients who relapsed after prior interferon monotherapy achieved a SVR when retreated with standard interferon plus ribavirin, and preliminary results show a SVR rate of about 32-50% for those treated with peginterferon plus

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proximately 15% of nonresponders achieved a SVR when retreated with combination therapy.<sup>1</sup> Overall, then, retreatment with standard interferon plus ribavirin benefits no more than about 15% of patients who did not respond to initial interferon monotherapy (see **Table 3**).

Another approach to retreatment is the use of high-dose induction interferon plus

feron followed by standard doses of interferon plus ribavirin. There are few studies of high-dose induction interferon in patients who have not responded to previous HCV therapy. A.H. Malik and colleagues studied 25 interferon monotherapy nonresponders randomized to receive one of two interferon regimens.<sup>8</sup> One group was treated with 10 MU of standard interferon daily for 10 days,

in people who did not respond to prior therapy with standard interferon with or without ribavirin. M. Buti and colleagues found that previously untreated patients with genotype 1 HCV who received high-dose peginterferon alfa-2b (3 µg/kg) experienced a significantly greater reduction in viral load over 48 hours and greater HCV RNA clearance at week 12, compared with those who

ribavirin. Among nonresponders to interferon monotherapy, 13-15% of patients achieved a SVR when retreated with standard interferon plus ribavirin, while 25-40% achieved a SVR when retreated with peginterferon plus ribavirin. Early data suggests that only about 10% of patients who did not initially respond to combination therapy with standard interferon plus ribavirin will respond to peginterferon plus ribavirin.

Since many nonresponders do not achieve a SVR even after retreatment with the best currently available therapies, management of nonresponders should include determining who is most likely to be successfully retreated and whether nonresponders can benefit from further therapy. Retreatment with peginterferon plus ribavirin—or experimental regimens—generally should be reserved for patients with favorable factors that predict SVR, such as prior relapse (as opposed to nonresponse), previous therapy with interferon monotherapy (as opposed to combination therapy), partial virological response (significant decrease in HCV RNA) during initial therapy, lower HCV viral load, and/or genotypes 2 or 3. Tolerance of and adherence to prior therapy should also be taken into account, as should the severity of underlying liver disease.

Patients with advanced liver fibrosis or cirrhosis (stage 3 or 4 fibrosis as determined by a liver biopsy) have progressed further along in the course of their disease, and are at greater risk for developing decompensation or end-stage liver failure in the subsequent 5-10 years. Such people are candidates for additional treatment, including experimental therapies. On the other hand,

patients with only mild to moderate (stage 0-2) fibrosis can generally afford to wait for newer developments in therapy, although their liver health should be monitored on an ongoing basis.

Maintenance therapy with low-dose peginterferon may reduce the risk of developing decompensated cirrhosis and liver cancer (hepatocellular carcinoma) in people with advanced fibrosis. It has been observed that up to 40% of these patients can experience a histological response (improvement in liver tissue damage) even if they do not achieve an undetectable viral load. Several studies are underway looking at whether long-term peginterferon monotherapy is a beneficial option for people with advanced liver disease. ■ ■ ■

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