Clinical Roundtable Monograph

Challenges in the Treatment of HCV Infection: Overcoming Viral Relapse After Standard Therapy

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Abstract

Standard treatment for hepatitis C viral infection in treatment-naïve patients consists of medical therapy with a combined regimen of pegylated interferon and ribavirin, with the goal of achieving viral eradication and sustained virologic response (SVR). However, up to 60% of patients do not attain SVR with this treatment. A subset of patients may achieve complete viral suppression but ultimately experience viral breakthrough during treatment, whereas others relapse after the end of treatment (EOT). Disease-related factors, including HCV genotype, initial viral load, and degree of hepatic fibrosis, as well as patient-related factors including body weight, ethnicity, adherence, and side effects can contribute to the likelihood of breakthrough and relapse. Early virologic response to treatment, particularly at Weeks 4 and 12, provide important predictive information on the likelihood of attaining SVR and can help guide treatment decisions. Clinicians should be aware of these factors and monitor patients carefully throughout treatment to ensure that patients are receiving the most appropriate therapy. For patients who develop viral relapse, several treatment options are currently available. Some patients may be candidates for retreatment with peginterferon/ribavirin if adherence was compromised during initial therapy. For others, an alternative treatment regimen with consensus interferon/ribavirin may be more effective. Nearly half of patients who relapse after HCV treatment attain SVR with daily consensus interferon/ribavirin when treated for 48 weeks. In order to understand strategies for treating the relapsed patient, an understanding of relapse physiology and the ability to predict relapse before and during treatment are necessary. Further, optimal retreatment strategies for these patients must be understood.

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Understanding Relapse Physiology

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Mechanism of Action of Peginterferon

Hepatitis C virus (HCV) infection is characterized by an ability to evade the host immune system and interfere with innate interferon (IFN)-based defense strategies.[1] However, HCV also promotes IFN expression, resulting in host defense against HCV. An understanding of this process at the molecular level helps illuminate the mechanism of action of interferon as antiviral treatment.

In hepatocytes, the presence of HCV double-stranded RNA results in the activation of two major molecular pathways of host defense: Toll-like receptor 3 (TLR-3) and retinoic acid-inducible gene I (RIG-I).[2] The activation of these innate sensing receptors results in the phosphorylation of interferon-regulating factors, which then translocate to the nucleus and promote the production of IFN-α/β.[3] The synthesis of IFN-α/β induces other cascades resulting in the activation of signal transducers and activators of transcription (STAT) proteins, MAP kinases, and the PI3 kinase/mTOR pathway (Figure 1).[4] This ultimately results in the induction of approximately 100 interferon-stimulating genes (ISG).[2] Although many ISGs have yet to be described, in general, these genes encode proteins that create a general antiviral state in infected, as well as neighboring uninfected, cells.

In addition to its effects on the innate immune system, IFN treatment also affects the adaptive immune response. IFNs upregulate the presentation of HCV peptides on the cell surface of hepatocytes and other antigen-presenting cells such as dendritic cells and macrophages.[5] IFN activates cytotoxic T-cells and natural killer cells, leading to the clearance of virally infected cells and, ultimately, a sustained virologic response (SVR).[6,7]

Mechanism of Action of Ribavirin

The addition of ribavirin to IFN is standard in the treatment of HCV. Although the molecular mechanism of action of ribavirin is not fully understood, it is known that ribavirin plays a key role in enhancing the efficacy of IFN and reducing the likelihood of relapse. This guanosine analog has some activity against DNA and RNA viruses, though it has minimal effect on HCV when used as monotherapy. It has been proposed that ribavirin acts as an immunomodulator by shifting the adaptive immune response towards an inflammatory antiviral Th1-type response, which improves the second-phase clearance of infected hepatocytes by IFN.[8] Ribavirin may also increase viral RNA mutagenesis, which decreases viral fitness and activity.[9]

Patterns of Viral Response

Viral kinetics studies have revealed two main phases of viral decline following antiviral treatment with interferon/ribavirin. The first phase, which occurs during the first 1–2 days after interferon administration, is a result of the direct antiviral effects of IFN—affecting both viral clearance and inhibition of viral replication.[10]

The second phase of viral decline, which occurs during the first month of treatment, is a result of the antiviral treatment on the adaptive immune response. The extent of the second-phase viral decline differs substantially across patients. The most desirable outcome is a rapid virologic response (RVR), defined as the complete eradication of virus by Week 4 as determined by achieving negative HCV RNA using a sensitive PCR technique. Achievement of RVR is associated with an 85–90% SVR rate.[11]

The next important landmark in viral kinetics is determined at Week 12. If patients attain an early virologic response (EVR), defined as a greater than 2 log reduction in HCV RNA by Week 12, treatment is continued. However, if they do not reach this benchmark, the treatment may be stopped or a different interferon used, as the likelihood of attaining viral clearance at the end of treatment or SVR is negligible. Recently, the definition of EVR was further categorized into a partial EVR (pEVR), defined as having a greater than 2 log response by Week 12, but with detectable HCV RNA, and a complete EVR (cEVR), defined as negative HCV RNA by Week 12 as measured by a sensitive assay. Published studies indicate that among patients who complete 48 weeks of antiviral therapy, the SVR rate among those who achieve a cEVR is 50–70%, as opposed to less than 10% SVR seen in patients with a pEVR.[12] Patients failing to achieve cEVR had dramatically reduced chances of SVR.[13,14]

Subsequently, HCV RNA levels are generally assessed every 3 months. The presence of detectable HCV RNA at any point after 3 months is an indicator to either stop treatment or switch to a different regimen. Certainly, the presence of HCV RNA at 6 months indicates that the

Figure 1. Mechanism of interferon antiviral activity.
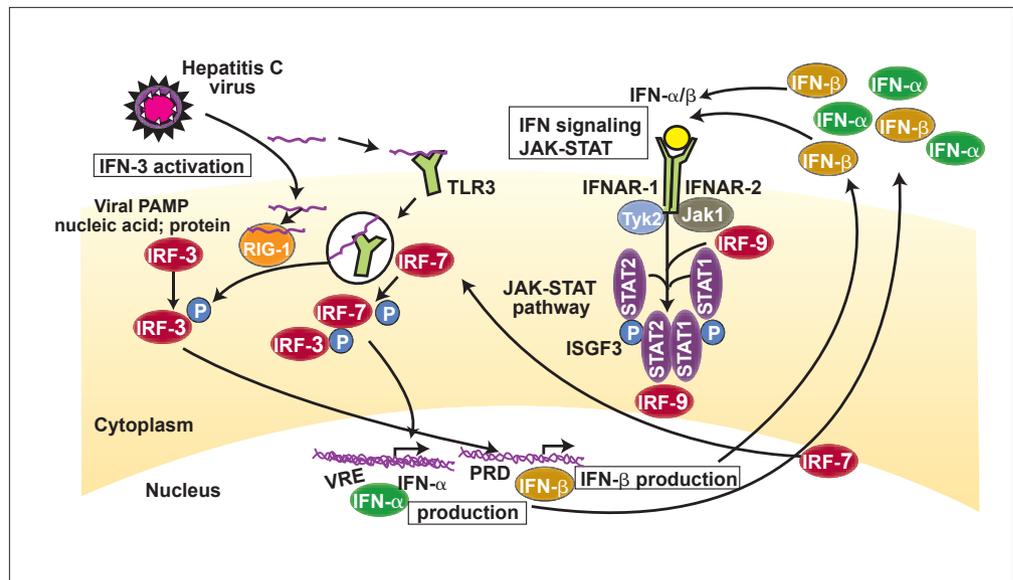
current treatment regimen should be stopped. Final virologic response to treatment is determined at Week 48. For patients with undetectable HCV RNA at the end of treatment, HCV RNA levels are assessed again at Week 72 to determine whether SVR has been attained. In the overwhelming majority of cases, patients who attain SVR will not develop progressive liver disease and recurrence of HCV in these patients is extremely rare.[15-17] A recent study showed that most virologic relapses occur during the first 3 months after the end of treatment, suggesting that it may not be necessary to wait until the traditional 6-month follow-up to detect a relapse. However, the optimal interval between end-of-treatment and SVR assessment is currently under review.

Occurrence of Viral Breakthrough

Viral breakthrough refers to the reemergence of detectable RNA during treatment. Because noncompliance is a possible cause of viral breakthrough, clinicians should always assess for noncompliance in patients who experience breakthrough. Reductions in the dosage of medications due to side effects or hematologic effects can also cause viral breakthrough. HCV RNA levels should be checked periodically if any dose adjustments are needed during the latter half of the treatment period. DiGiorno and colleagues released data concerning viral breakthrough, known as transcription-mediated amplification (TMA) "blips." These "blips" were defined as the presence of TMA-detectable viral positivity after achieving PCR-confirmed viral suppression while on therapy. With these occurrences, a higher incidence of relapse was seen, especially in genotype 1 patients.[18]

Preventing Viral Relapse

One important advance in relapse prevention is the finding that maintaining a high ribavirin dose (11–13 mg/kg/day) reduces the risk of relapse.[19,20] Another area of investigation is the optimal duration of treatment, particularly for patients with a slow virologic response, defined as attainment of pEVR by Week 12 and negative HCV RNA by 6 months. For certain slow responders, some literature supports extending treatment from 48 weeks to 72 weeks, with SVR rates reported in 7.5–38% of patients.[13,21]

References

1. Foy E, Li K, Sumpter R Jr, et al. Control of antiviral defenses through hepatitis C virus disruption of retinoic acid-inducible gene-I signaling. *Proc Natl Acad Sci U S A.* 2005;102:2986-2991.
2. Kanda T, Steele R, Ray R, Ray RB. Hepatitis C virus infection induces the beta interferon signaling pathway in immortalized human hepatocytes. *J Virol.* 2007;81:12375-12381.
3. Gale M Jr, Foy EM. Evasion of intracellular host defence by hepatitis C virus. *Nature.* 2005;436:939-945.
4. Pilz A, Ramsauer K, Heidari H, Leitges M, Kovarik P, Decker T. Phosphorylation of the Stat1 transactivating domain is required for the response to type I interferons. *EMBO Rep.* 2003;4:368-373.
5. Cheng PN, Wei YL, Chang TT, Chen JS, Young KC. Therapy with interferon-alpha and ribavirin for chronic hepatitis C virus infection upregulates membrane HLA-ABC, CD86, and CD28 on peripheral blood mononuclear cells. *J Med Virol.* 2008;80:989-996.
6. Caetano J, Martinho A, Paiva A, Pais B, Valente C, Luxo C. Differences in hepatitis C virus (HCV)-specific CD8 T-cell phenotype during pegylated alpha interferon and ribavirin treatment are related to response to antiviral therapy in patients chronically infected with HCV. *J Virol.* 2008;82:7567-7577.
7. Bonavita MS, Franco A, Paroli M, et al. Normalization of depressed natural killer activity after interferon-alpha therapy is associated with a low frequency of relapse in patients with chronic hepatitis C. *Int J Tissue React.* 1993;15:11-16.
8. Hultgren C, Milich DR, Weiland O, Sällberg M. The antiviral compound ribavirin modulates the T helper (Th) 1/Th2 subset balance in hepatitis B and C virus-specific immune responses. *J Gen Virol.* 1998;79:2381-2391.

9. Lutchman G, Danehower S, Song BC, et al. Mutation rate of the hepatitis C virus NS5B in patients undergoing treatment with ribavirin monotherapy. *Gastroenterology*. 2007;132:1757-1766.

10. Dahari H, Ribeiro RM, Perelson AS. Triphasic decline of hepatitis C virus RNA during antiviral therapy. *Hepatology*. 2007;46:16-21.

11. Yu JW, Wang GQ, Sun LJ, Li XG, Li SC. Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. *J Gastroenterol Hepatol*. 2007;22:832-836.

12. Davis GL, Wong JB, McHutchison JG, et al. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology*. 2003;38:645-652.

13. Mangia A, Minerva N, Bacca D, et al. Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. *Hepatology*. 2008;47:43-50.

14. Berg T, von Wagner M, Nasser S, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology*. 2006;130:1086-1097.

15. Shiratori Y, Imazeki F, Moriyama M, et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Intern Med*. 2000;132:517-524.

16. Lau DT, Kleiner DE, Ghany MG, et al. 10-year follow-up after interferon-alpha therapy for chronic hepatitis C. *Hepatology*. 1998;28:1121-1127.

17. Swain M, Lai MY, Shiffman ML, et al. Durability of sustained virological response (SVR) after treatment with peginterferon alfa-2a alone or in combination with ribavirin: results of an ongoing long-term follow-up study. *Hepatology*. 2004;40(suppl 1): 400A.

18. DiGiorno C, Deng K, Casellas A, et al. The "TMA blip": clinical significance of transient positivity of hepatitis C virus (HVCV) transcription-mediated amplification (TMA) during periods of polymerase chain reaction (PCR) negativity on anti-viral therapy. Presented at Digestive Disease Week. May 17-22, 2008, San Diego, Calif. Abstract S1015.

19. Marotta P, Feinman SV, Ghent C, et al. Final results of the Canadian POWeR (Pegetron Prospective Optimal Weight-based Dosing Response) program: sustained virologic response (SVR) to weight-based peginterferon alfa-2b + ribavirin in a large, mixed, community and academic observational study. Poster presented at: the 58th Annual Meeting of the American Association for the Study of Liver Diseases. November 2-6, 2007, Boston, Massachusetts.

20. Jacobson IM, Brown RS Jr, Freilich B, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology*. 2007;46:971-981.

21. Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. *Hepatology*. 2007;46:1688-1694.

Predicting Relapse Before and During Treatment

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Patients predisposed to the development of relapse after antiviral treatment for chronic HCV can often be identified based on factors present before treatment or based on their response to treatment. Historically, 20–30% of patients will relapse after obtaining an end-of-treatment response.[1] Identifying these patients early allows clinicians to maximize outcomes by ensuring that they are carefully monitored for viral relapse, and that alternatives of altered dosing or different interferon formulations can be administered as early as possible.

Disease-Related Factors Affecting Responses to Treatment

Several disease-related factors contribute to the risk of relapse in patients undergoing treatment for HCV infection. These factors should all be considered when discussing with patients the risks and benefits of initiating treatment.

Genotype 1 HCV is the most common genotype in the United States, as well as the most difficult to treat.[2] Another important disease related-factor is initial viral load, which is an independent initial predictor of treatment response. In a recently released co-infected HIV/HCV study, patients with viral loads greater than 500,000 IU/mL at the start of treatment (baseline) were five times more likely to relapse if end-of-treatment negativity were achieved, compared to patients with low viral loads.[3] Furthermore, patients with positive viremia after Week 4 following initiation of therapy were three times more likely to relapse than those who achieved an RVR.[3] The impact of viral load appears to be consistent across all genotypes.[4]

The degree of hepatic fibrosis must also be factored into likelihood of response to antiviral treatment. In one study of patients with genotype 1 or 4 HCV, a low fibrosis score was associated with likelihood of RVR and an SVR rate of 80%.[5] In another study of patients with genotype 1 infection, SVR rates were higher among patients without cirrhosis versus those with cirrhosis (41% vs. 34%).[6] In this population, ribavirin reductions are often necessary due to a weak hematologic profile at baseline, further contributing to the high relapse rate. Interestingly, baseline levels of the cytokine tumor necrosis factor (TNF) and IL-8 in the serum also appear to predict for a higher SVR rate and a lower virologic relapse rate.

Patient-Related Factors Affecting Responses to Treatment

Body weight is an important patient factor that affects likelihood of response to therapy. Patients weighing more than 75 kg are significantly less likely than lighter patients to respond to peginterferon/ribavirin.[7] This may relate to an increased rate of nonalcoholic fatty liver disease, or an increased rate of fibrosis due to cholestatic and fatty liver disease. However, the effect of body weight on treatment responses remains after controlling for these factors and is thus not fully understood.

Race, ethnicity, and gender also affect responses to treatment. African American patients are the least likely to respond to peginterferon/ribavirin, followed by Hispanics, and nonhispanic whites, who have the best response. Men are overall less likely to respond than women.

Another important patient-related factor that affects treatment responses is adherence, which may differ among patients based on various factors. The emergence of treatment-related side effects, such as anemia, neutropenia, thrombocytopenia, and neuropsychiatric effects, can have a profound effect on adherence. Patients with an increased number of side effects are more likely to have decreased adherence or to require dose reductions. Therefore, the emergence of side effects is an important predictive factor of treatment outcomes. However, all patients who undergo treatment with peginterferon/ribavirin should be monitored closely and side effects should be managed aggressively in order to minimize dose reductions.

Adherence is an issue in the administration of both peginterferon and ribavirin. In fact, early during the treatment course, adherence to ribavirin and the need for ribavirin dose reductions have an effect on SVR, particularly in the first 24 weeks of therapy and prior to the patient achieving viral negativity.[8] However, another study reported that ribavirin dose reductions do not affect SVR rates until the cumulative ribavirin dosage declines

below 60%.[9] A ribavirin convenience dose pack is now available which has been shown to improve adherence in HCV patients.[10]

Predicting Outcomes Based on Responses to Treatment

Berg and colleagues[11] theorized that the presence of residual viremia at Week 12 may influence treatment outcomes of SVR. In their prospective trial, 433 patients were randomized to receive either 48 weeks of therapy, or a treatment regimen based on time of achieving viral negativity. As seen in other trials, patients achieving RVR had relapse rates below 10%. However, in patients with detectable HCV RNA at Week 12, relapse rates can be greater than 50%.

End-of-treatment responses are an important predictor of treatment outcomes. Patients who do not attain negative HCV RNA by the conclusion of treatment do not achieve SVR.[12] Therefore, clinicians should confirm HCV RNA negativity at the end of treatment, and 6 months after the end of treatment, in order to confirm an SVR.

As discussed previously, responses to peginterferon/ribavirin early during the treatment period are one of the most important predictors of SVR. Careful monitoring of viral response on therapy is therefore important for predicting responses, particularly in patients who develop significant side effects and have difficulty with adherence.

We may discuss with these patients the risk/benefit of continued treatment based on the patients' virologic response and thus their expected likelihood of SVR.

References

1. Davis GL, Wong JB, McHutchison JG, et al. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology*. 2003;38:645-652.
2. Rustgi VK. The epidemiology of hepatitis C infection in the United States. *J Gastroenterol*. 2007;42:513-521.
3. Nunez M, Marino A, Miralles C, et al. Baseline serum hepatitis C virus (HCV) RNA level and response at week 4 are the best predictors of relapse after treatment with pegylated interferon plus ribavirin in HIV/HCV-coinfected patients. *J Acquir Immune Defic Syndr*. 2007;45:439-444.
4. Shepherd J, Brodin H, Cave C, et al. Pegylated interferon alpha-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess*. 2004;8:1-125.
5. Westin J, Ydreborg M, Islam S, et al. A non-invasive fibrosis score predicts treatment outcome in chronic hepatitis C virus infection. *Scand J Gastroenterol*. 2008;43:73-80.
6. Lee SS, Bain VG, Peltekian K, et al. Treating chronic hepatitis C with pegylated interferon alfa-2a (40 KD) and ribavirin in clinical practice. *Aliment Pharmacol Ther*. 2006;23:397-408.
7. Reddy KR, Govindarajan S, Marcellin P, et al. Hepatic steatosis in chronic hepatitis C: baseline host and viral characteristics and influence on response to therapy with peginterferon alpha-2a plus ribavirin. *J Viral Hepat*. 2008;15:129-136.
8. Reddy KR, Shiffman ML, Morgan TR, et al. Impact of ribavirin dose reductions in hepatitis C virus genotype 1 patients completing peginterferon alfa-2a/ribavirin treatment. *Clin Gastroenterol Hepatol*. 2007;5:124-129.
9. Yamada G, Iino S, Okuno T, et al. Virological response in patients with hepatitis C virus genotype 1b and a high viral load: impact of peginterferon-alpha-2a plus ribavirin dose reductions and host-related factors. *Clin Drug Investig*. 2008;28:9-16.
10. Palmer M. Improvement in treatment adherence in patients with chronic hepatitis C. *Pract Gastroenterol*. 2008;32:31-38.
11. Berg T, von Wagner M, Nasser S, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology*. 2006;130:1086-1097.
12. Strader DB, Wright T, Thomas DL, Seeff LB. AASLD Practice Guideline: Diagnosis, management, and treatment of hepatitis C. *Hepatology*. 2004;39:1147-1171.

Treatment Options for Relapsing Patients

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Several treatment options are currently available for patients who develop viral relapse after antiviral therapy for HCV. For patients who develop relapse following peginterferon/ribavirin therapy, retreatment with the same regimen may be appropriate if adherence was compromised during initial therapy. Between 30% and 40% of these patients will respond to retreatment, with responses varying based on patient factors such as genotype and degree of fibrosis.[1]

Role of Novel Agents for Treating HCV Viral Relapse

The approval of effective new agents, such as the investigational class of protease and polymerase inhibitors, could be a valuable addition for the treatment of patients with viral relapse. However, studies of these agents are still ongoing, and the efficacy of protease/polymerase inhibitors in relapsed patients remains to be seen. Potentially substantial issues of cost and toxicity must also be considered with these agents. Most likely, a select subpopulation of patients will benefit from their use.

Role of Low-Dose Maintenance Interferon

Low-dose maintenance interferon had been proposed as a way to improve clinical outcomes in patients who do not respond to peginterferon/ribavirin. The HALT-C study evaluated this approach, randomizing 1,050 patients with advanced fibrosis to peginterferon alfa-2a at 90 µg/week for 3.5 years versus no treatment.[2] The investigators found that low-dose interferon provided no reduction in progression of liver disease, defined as death, hepatocellular carcinoma, hepatic decompensation, or an increase in Ishak fibrosis score of 2 or greater among patients with bridging fibrosis at baseline. Thus, although laboratory parameters did improve with treatment, clinical outcomes were not affected. Based on these outcomes, maintenance low-dose interferon is not recommended for nonresponding or relapsing patients.

Consensus Interferon in Relapsing Patients

Another treatment option for patients with viral relapse is consensus interferon. This highly potent agent permits administration of a 100% biologically-active molecule, compared with peginterferon, which consists partially of the inert pegylated molecule. Consensus interferon has shown a superior ability to induce the cellular biological events required to generate an adequate antiviral response.[3] Multiple studies have demonstrated the activity of consensus interferon both as monotherapy and in combination with ribavirin. A pilot study evaluating consensus interferon as monotherapy in 24 patients showed an SVR rate of 42% among previous relapsers.[4] Multiple publications have since confirmed the activity of consensus interferon in relapsed patients (Table 1).

One recent study suggests that consensus interferon may be more effective than peginterferon in patients with viral relapse. In the study, Kaiser and colleagues randomized 120 HCV relapse patients (76% genotype 1) to retreatment with consensus interferon/ribavirin or peginterferon/ribavirin for 72 weeks.[5] Consensus interferon/ribavirin was associated with a significantly higher SVR rate compared with peginterferon/ribavirin (69% vs. 42%; P<.05), providing a substantial 20–25% increase in the SVR rate. Although no other head-to-head studies have been conducted, other independent trials of the two regimens have shown similar SVR rates.

Ghalib and coworkers took a similar group of peginterferon/ribavirin relapsers and subsequently retreated them with consensus interferon and ribavirin daily for 48 weeks. Overall SVR in this population was 47% (9/19). In addition, rates of SVR were improved in patients achieving viral negativity at week 12 (66%) versus viral positivity (0%). Consensus interferon was well tolerated by this population.[6]

Our group evaluated consensus interferon in 25 patients with HCV (90% genotype 1) who relapsed after peginterferon/ribavirin. Patients received 15 µg consensus interferon daily for 48 weeks. The SVR rate was 47% among genotype 1 patients and 55% in the overall population, similar to what had been observed in other studies (Figure 1).[7]

The duration of therapy for nonresponding and relapsing patients is not as clear-cut as it is for treatment-naive patients. Some patients may benefit from a longer-term treatment. For example, when we utilize consensus interferon, we would prefer to see a 2-log or greater decline in HCV RNA by Week 12 and HCV RNA negativity by Week 24 in order to continue treatment.[12] In our practice, we continue patients on treatment for at least 48 weeks after attaining HCV RNA negativity. The treatment duration therefore varies according to when the patient attains

Table 1. Response to Consensus Interferon-based Therapies Among Relapsers on Prior Therapy

| Dose and Length of Therapy	N	SVR	Reference
One year daily CIFN 15 mcg monotherapy for relapsers to prior interferon treatment	6	4/6 (66%)	Aladag et al.[8]
CIFN 15 mcg three times/week for 24 or 48 weeks	75 (33 and 42)	28% (24 weeks) vs 58% (48 weeks)	Heathcote et al.[9]
CIFN 9 mcg 5 days/week for 36 weeks for relapsers to prior therapy	12	42%	Barbaro et al.[4]
One year CIFN (9 or 18 mcg) in combination with ribavirin (800–1,200 mg/day) for relapsers to prior interferon treatment	45 (22 and 23)	27.3% (9 mcg) vs 26.1% (18 mcg)	Alaimo et al.[10]
CIFN 9 mcg/day for 24 weeks	40	58%	Miglioresi et al.[11]
CIFN 15 mcg/day plus weight based ribavirin for 48 weeks	19	47%	Ghalib et al. (abstract)[6]
CIFN 9 mcg/day and ribavirin vs Peg IFN/ribavirin for 72 weeks	120	69% vs 42%	Kaiser et al. (abstract)[5]
CIFN 15 mcg/day and weight-based ribavirin	22	55%	Sjogren and Sjogren[7]
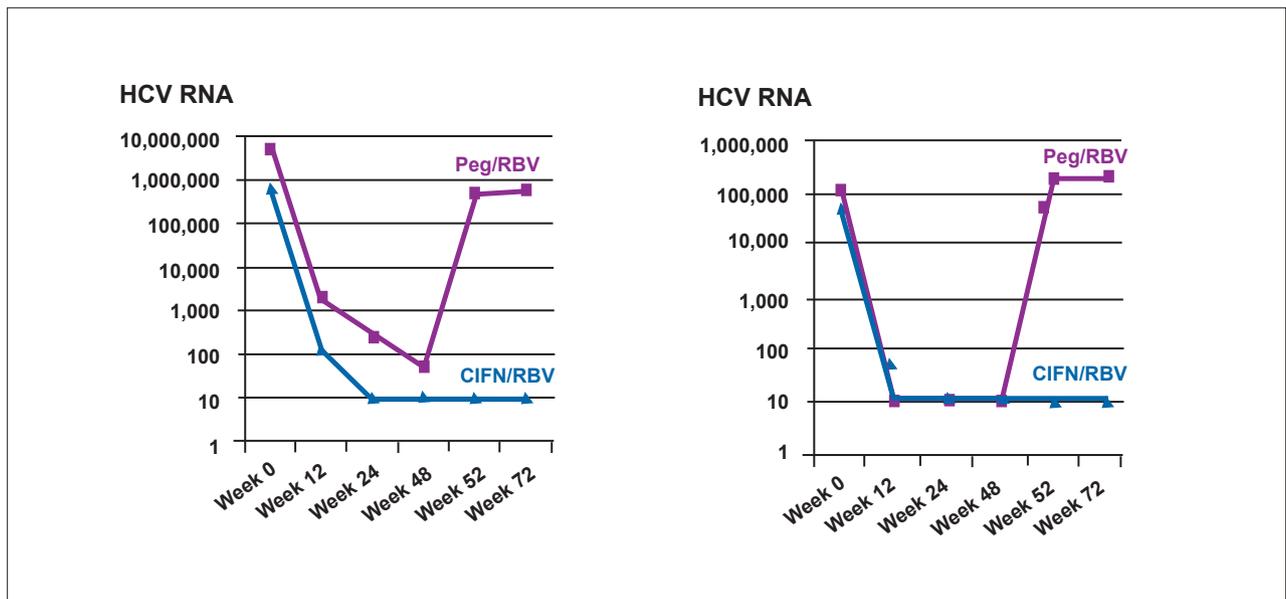
Figure 1. Depiction of viral load levels in two subjects who relapsed after 48 weeks of treatment with standard therapy (pegylated interferon/ribavirin; red) and successful response when re-treated with 48 weeks of daily consensus interferon plus ribavirin (blue).

Data from Sjogren and Sjogren.[7]

negative HCV RNA. Based on results in treatment-naive patients, those who attain negative HCV RNA by Week 12 should receive 60 weeks of treatment, whereas patients who attain negative HCV RNA by Week 24 would receive 72 weeks of treatment.[13] We have used these guidelines in our practice based on the literature and clinical experience. Nonetheless, clinical trial data clearly support the role of consensus interferon in the treatment of patients with viral relapse following peginterferon/ribavirin treatment for HCV.

References

1. Poynard T, Schiff E, Terg R, et al. Sustained viral response (SVR) is dependent on baseline characteristics in the retreatment of previous alfa interferon/ribavirin (I/R) nonresponders (NR): final results from the EPIC3 program. Presented at the 43rd Annual Meeting of the European Association for the Study of the Liver. April 23-27, 2008, Milan, Italy.

2. Di Bisceglie AM, Shiffman ML, Everson GT, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med*. 2008;359: 2429-2441.

3. Fish EN, Banerjee K, Stebbing N. The role of three domains in the biological activity of human interferon-alpha. *J IFN Res*. 1989;9:97-114.

4. Barbaro G, Barbarini G. Consensus interferon for chronic hepatitis C patients with genotype 1 who failed to respond to, or relapsed after, interferon alpha-2b and ribavirin in combination: an Italian pilot study. *Eur J Gastroenterol Hepatol*. 2002;14:477-483.

5. Kaiser S, Lutze B, Sauter B, et al. Retreatment of HCV genotype 1 relapse patients to peginterferon/ribavirin therapy with an extended treatment regimen of 72 weeks with consensus interferon/ribavirin versus peginterferon alfa/ribavirin. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Disease. November 2-6, 2007, Boston, Massachusetts.

6. Ghalib R, Levine C, Friedman D, et al. Consensus interferon plus ribavirin therapy in patients who are nonresponders or relapsers to prior peginterferon plus ribavirin therapy. Presented at the 38th Annual Digestive Disease Week. May 19-24, 2007, Washington, D.C.

7. Sjogren MH, Sjogren RW. Personal communication/manuscript in preparation.

8. Aladag M, Karasu Z, Wright H, Gurakar A. Daily Consensus interferon monotherapy in nonresponders or relapsers to a previous interferon regime: one year follow up after 48 weeks of treatment. *Turk J Gastroenterol*. 2006;17:35-39.

9. Heathcote J et al. Re-treatment of chronic hepatitis C with consensus interferon. *Hepatology*. 1998;27:1136-1143.

10. Alaimo G et al. Different doses of CIFN plus ribavirin in patients with hepatitis C virus genotype 1 relapsed after monotherapy: A randomized trial. *World J Gastroenterol*. 2006;14:6861-6864.

11. Miglioresi L et al. Consensus interferon versus interferon alpha-2b plus ribavirin in patients with relapsing infection. *Hepatol Res*. 2003;27:253-259.

12. Bacon BR, Regev A, Ghalib RH, et al. The DIRECT Trial (Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy): Treatment of nonresponders to previous pegylated interferon plus ribavirin: sustained virologic response data. Presented at the 58th Annual Meeting of the American Association for the Study of Liver Disease. November 2-6, 2007, Boston, Massachusetts.

13. Mangia A, Minerva N, Bacca D, et al. Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. *Hepatology*. 2008;47:43-50.