Clinical Roundtable Monograph

The Role of Consensus Interferon in the Current Treatment of Chronic Hepatitis C Viral Infection

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Abstract

The current standard-of-care for chronic hepatitis C viral infection is treatment with pegylated interferon (PegIFN) plus ribavirin for 24 to 48 weeks. Approximately 50% of HCV-infected patients achieve a sustained viral response (SVR) to this treatment. However, the remaining patients either respond during treatment but relapse upon treatment cessation, respond minimally, or do not respond at all. Much research effort has been expended in attempting to predict those patients who will achieve viral eradication with PegIFN/ribavirin treatment, and it is now clear that those who have either a rapid virologic response (RVR) by week 4 of treatment or a complete early virologic response (cEVR, HCV RNA qualitative negative) by week 12 will go on to achieve SVR at very high rates (70%–90%). Several trials have been completed in patients that fail to achieve RVR or cEVR. These trials include strategies of extending duration of therapy, induction regimens, or retreatment with similar and dissimilar alfa interferons. A recent study of 696 genotype 1 patients treated with both PegIFN and weight-based ribavirin revealed that only 1.6% (4/246) of patients without RVR or cEVR achieved SVR. Consensus interferon, a wholly synthetic interferon-alfa, is one of the agents that has been utilized in patients that fail treatment with PegIFN/ribavirin. This molecule has been demonstrated to have a very high affinity for the interferon-alfa receptor, and laboratory studies have demonstrated that it has high levels of antiviral activity. In order to optimally utilize consensus interferon, it is important to understand its unique mechanism of action. In addition, the latest research showing the importance of achieving RVR or cEVR should be reviewed, along with strategies for utilizing consensus interferon in re-treatment, or more specifically upon identification of on-treatment failure in historically difficult-to-treat patients.

GASTROENTEROLOGY&HEPATOLOGY ™

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Understanding Consensus Interferon

Eleanor N. Fish, PhD

Interferons (IFN) belong to the cytokine family of proteins that help regulate immunity. They are produced by the body in response to viral infections.[1] IFNs are classified according to their distinct cognate receptors. The IFN-αs and IFN-β are classified as type I, and exhibit antiproliferative and antiviral activities.[2,3] IFN-γ is classified as type II; it has more potent immunomodulatory properties than the type I IFNs.[4]

In looking at the type I IFNs in humans, there are 14 IFN-α subtypes, a single IFN-β subtype, as well as IFN-ε, IFN-ω, IFN-δ, IFN-κ, and IFN-τ. Interestingly, all of these bind to and activate the same receptor complex, called IFN-α/β receptor (IFNAR), which is composed of 2 transmembrane subunits (IFNAR1 and IFNAR2).[5] In the 1980s, the IFN-α subtypes were evaluated for bioactivity, and comparisons were made among subtypes. In cell culture models, all of the IFN-α subtypes showed antiviral activity and growth inhibitory activity, and all exhibited a number of immunomodulatory functions. In addition, all of the subtypes were able to activate natural killer cell (NKC) activity, and were able to skew naïve T-cells toward the T_H1 lineage. The notable difference among the IFN-α subtypes was their potency in producing the various effects.[6]

A number of research groups developed interest in the differential potency of the IFN-α subtypes. Upon close analysis, the subtypes were found to exhibit a high degree of identity at the amino acid level such that minor amino acid changes were able to produce dramatic changes in potency. Through the use of mutational studies, it was determined that there were three regions amongst all the IFN-α subtypes that appeared to contribute to biological activity.[7] These three regions mediate binding of the IFNs to IFNAR, and it was found that the stronger the affinity of a particular IFN-α subtype for IFNAR, the stronger its biological potency.[7] For example, IFN-α1 binds with relatively weak affinity to IFNAR and exhibits relatively weak antiviral and growth inhibitory activities, whereas IFN-α2 binds with much stronger affinity to the same receptor and exhibits much stronger bioactivity. A consensus sequence was then determined for the IFN-α subtypes. This was accomplished by aligning the 166 amino acids for each of the 14 IFN-α subtypes, and then noting the most frequently represented amino acid at each position. Using recombinant technology, a novel synthetic IFN was constructed based on this consensus amino acid sequence. This "consensus interferon" molecule, IFN alfacon-1, was examined for its ability to bind to IFNAR, and found to have the highest affinity among all the known IFN-α molecules, including hybrid variants, the recombinants, and the natural subtypes. Most importantly, that higher affinity translates to a higher biopotency—approximately 10-fold more active than any other IFN.[8]

Consensus Interferon Versus Pegylated Interferon: Understanding the Difference

When used as pharmaceutical agents, type I IFNs are unstable and have a short half-life of 6–20 hours. This typically requires three-times-per-week dosing. In order to stabilize the molecule and allow once weekly dosing, pegylated versions of IFN (PegIFN) have been produced. Pegylation is the process whereby a polyethylene glycol polymer is attached to the IFN molecule. This increases the half-life, but pegylation comes with a price in terms of potency and side effects: if the pegylated moiety is added to a region that is specifically involved in contacting the receptor, then that particular IFN molecule loses biological activity. Indeed, the pegylation process has been demonstrated to result in a 60–90% loss in activity of IFN.[9-11] This effect is also observed when comparing PegIFN dosing to prior standard dosing, as 150–180 µg of PegIFN is 3-to-4–fold the dose of 3 MU three-times-weekly (3 MU thrice weekly is approximately 45 µg per week). When used therapeutically, patients receive potentially biologically inactive PegIFN along with the biologically active PegIFN, which may be associated with increased levels of adverse effects.[12] Consensus IFN (IFN alfacon-1) is not pegylated, and each molecule is biologically active.

Consensus Interferon Mechanism of Action

When the human body is infected by a virus, the first line of defense is the innate immune response. The innate immune response is a nonspecific surveillance system that relies upon pattern recognition receptors (PRRs) to recognize molecules that are broadly shared by pathogens but distinguishable from host molecules. These molecules include bacterial carbohydrates, bacterial or viral DNA or RNA, peptidoglycans and lipotechoic acids from gram positive bacteria, N-formylmethionine, lipoproteins, and fungal glucans. Upon pattern recognition, the PRRs trigger intercellular signaling cascades.[13] One of the key endpoints for these intercellular signaling cascades is an upregulation of IFN production, making IFN a critical part of the host immune response.

IFNs are able to exert antiviral activity regardless of the virus being targeted. Upon binding to IFNAR, IFNs trigger intercellular signaling pathways that upregulate cellular production of interferon induced proteins (IIPs). These proteins have a number of effects and are able to disrupt different stages of the viral replicative cycle.[14] First, IIPs can prevent viral entry into a cell by ordering the cytoskeleton of that cell. Second, if viruses do enter a cell, IIPs can inhibit the uncoating of certain viruses, rendering them unable to take advantage of the host cell machinery and replicate. Third, IIPs can inhibit viral RNA translation, which blocks production of the viral proteins. Lastly, IIPs can block already-assembled virus from exiting the cell. It becomes clear, now, why the potency of IFNs is directly proportional to their ability to bind to the IFNAR. Stronger binding to the IFNAR more effectively triggers the production of IIPs, resulting in stronger antiviral activity. In the context of HCV, IFN is able to interfere with translational events associated with HCV replication. Two key IIPs that combat HCV replication are protein kinase R (PKR) and p56, which exert their effects by blocking translation initiation.[15]

How, then, does HCV develop resistance to IFN? The virus encodes proteins in its genome that are able to interfere with some of the IFN-inducible effects that are mediated by PKR[15]; however, the efficacy of HCV's evasive maneuvers may not necessarily completely override the effects of IFN treatment. In a scenario where one is treating with an IFN molecule that only weakly activates PKR, HCV will effectively block the PKR-inducible events and thereby confer resistance to IFN treatment. In a scenario where one is treating with an IFN molecule that is very effective in rapidly inducing a large amount of PKR, the balance between the virus inhibitory/antagonistic effects and the IFN PKR-mediated effects are skewed in favor of the IFN.

Based on its high affinity for IFNAR, consensus IFN will activate IFNAR to invoke multiple signaling cascades, and, in the context of HCV, the strength of the signals provide for high levels of PKR and p56. This, in turn, will block HCV RNA translation and viral replication. In addition, IFN will upregulate both innate and adaptive immune responses to clear virus infection, targeting NK cells, B cells, and T cells.[3] Once again, the higher the affinity of the IFN molecule for cell surface IFNAR on these immune cells, the stronger the signaling output from the receptor and the more pronounced the effector function of that immune cell. Viewed altogether, consensus IFN is intrinsically more biopotent than other IFN-αs against HCV, based on its superior affinity for IFNAR.

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Defining Response and Predicting Outcomes With Interferon-based Therapies

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There is great interest among the HCV treatment community in predicting those patients who are most likely to achieve a complete and sustained virologic response (SVR) to IFN-based therapies. This interest stems from the desire to limit patient exposure to these drugs and their resultant side effects as well as limiting the cost associated with treatment. Thus, a number of studies have looked at patient response within the first 4–12 weeks of therapy as a predictor of eventual outcome. It is important to understand the various definitions of response and their prognostic value for SVR, defined as viral negativity through 6 months after treatment cessation.

Genotype 1 Patients

The commonly accepted definition of the early virologic response (EVR) was first published by Davis and colleagues in 2003.[1] In this retrospective analysis, Davis reviewed the registration trials for PegIFN-α2a and -α2b. Regardless of genotype, all patients were treated for 48 weeks with PegIFN and various doses of ribavirin. In these study cohorts, composed of 65--68% genotype 1 patients, those achieving an EVR (>2 log drop at week 12) had an overall SVR of 68%. However, the SVR was greater in those patients achieving a complete EVR (HCV RNA negative at week 12; 80%) when compared to those achieving a partial EVR (>2 log drop, continued viral positivity; 40%). Patients who did not reach EVR, however, did not respond to a further 9 months of PegIFN-α2b therapy. Approximately 75% of patients achieved EVR in this study. The investigators concluded that therapy can be confidently discontinued in patients who do not achieve EVR, a tactic that would have cut drug costs by more than 20% in their study.

In the past 2 years, the concept of rapid virologic response (RVR) has been introduced as a possible predictor for SVR as well.[2,3] An RVR is defined as an undetectable HCV RNA level as measured by PCR at week 4 of treatment. Note that this is different from EVR in that it does not consider log drop, but rather requires complete viral negativity. A retrospective analysis was performed by Jensen and colleagues on 729 patients treated with PegIFN-α2a and weight-based ribavirin (1,000–1,200 mg/day).[4] They showed that the SVR rate was 89% among patients with an RVR but ranged from only 16% to 44% among patients without an RVR.

Subsequently, Ferenci and colleagues[5] prospectively evaluated the efficacy of a shorter duration of treatment for patients infected with HCV genotypes 1 and 4 who achieve an RVR. A total of 516 patients infected with HCV genotype 1 or 4 were treated with PegIFN-α2a plus ribavirin (1,000–1,200 mg/day). At week 4, 150 patients (29%) had achieved an RVR. Although this patient population would normally be treated for 48 weeks, Ferenci and colleagues limited treatment to 24 weeks among the patients who had achieved an RVR, and found that the SVR rate was 80.4%. They concluded that a 24-week regimen of PegIFN-α2a plus ribavirin is appropriate for genotype 1 and 4 patients with a low baseline HCV RNA level who achieve an RVR by week 4 of therapy.

Additionally, Zeuzem and colleagues[6] compared relapse rates among patients infected with HCV genotype 1 who achieved an RVR on PegIFN/ribavirin therapy and those who did not. Of note, the patients in this study all had a low baseline viral load (600,000 IU/mL or less). A total of 235 patients were treated with PegIFN-α2b plus weight-based ribavirin (800–1,400 mg/day) for 24 weeks. The SVR rate was 50% in the intent-to-treat analysis, but those patients who had an RVR achieved an SVR rate of 89%. Therefore, the authors concluded that patients infected with HCV genotype 1, who have a low baseline HCV RNA concentration, can safely be treated for only 24 weeks when an RVR is achieved, although those who do not, should still be treated for a longer period of time.

Most recently, Mangia and colleagues[7] conducted a study of 696 treatment-naive genotype 1 patients treated with either PegIFN-α2a or -α2b plus weight-based ribavirin and divided them into two groups, one that received uniform standard treatment of 48 weeks and one that received treatment at variable lengths (24, 48, or 72 weeks) based on the on-treatment time interval until their first PCR measure of undetectable virus; patients achieving RVR at week 4 received 24 weeks total, patients achieving viral negativity at week 8 received 48 weeks of therapy, and patients achieving at least a 2 log drop or greater at week 12 continued on for 72 weeks of therapy. Among patients achieving an RVR, the overwhelming majority achieved an end of treatment response in both groups (95.1% and 96.8% in the 24-week and 48-week cohorts, respectively). However, relapse rates created a significant difference in SVR (77.2% and 87.0%, respectively). Thus, we might conclude

that patients with low viral load who achieve an RVR, consideration can be given to a 24-week course of therapy. However, the relapse rate among these patients is likely to be higher than in those receiving a standard course of therapy.

Based on this RVR data, there has been a resurgence in interest in studying the predictive value of an EVR more closely. Traditionally, an EVR has been defined as at least a 2 log drop in HCV RNA by week 12 of treatment; however, this broad definition also includes patients who have virus negativity at week 12. To be more precise, some investigators have proposed subdividing the EVR into a complete EVR (virus negativity at week 12) and a partial EVR (detectable HCV RNA levels at week 12 that are at least a 2 log drop from baseline), and there are now data to support this approach.

Marcellin and colleagues[8] retrospectively analyzed data from seven studies to determine the SVR rates among patients infected with HCV genotype 1 who had achieved an RVR, a complete EVR without RVR, or a partial EVR on treatment with PegIFN-α2a plus ribavirin for 48 weeks. Ribavirin dosages in these studies varied from 600 to 1,200 mg/day. They found that 12–36% of patients achieved an RVR, with corresponding SVR rates ranging between 66% and 91%. A complete EVR without RVR was achieved by 34–52% of patients overall, with corresponding SVR rates of 52% to 76%. In contrast, patients with a partial EVR had an SVR rate of only 27%.

Several studies have looked at extending the treatment duration from 48 to 72 weeks in an effort to improve SVR rates among genotype 1-infected patients, particularly those patients who do not achieve an RVR or complete EVR. In one study, Berg and colleagues[9] treated HCV genotype 1-infected patients with either 48 weeks (n=230) or 72 weeks (n=225) of treatment with PegIFN-α2a plus ribavirin (800 mg/day). There were no significant differences in end-of-treatment response and SVR rates between the two groups in the intent-to-treat analysis, and no significant differences between groups for the patients who had achieved an RVR or a complete EVR. Interestingly, however, patients who were still HCV RNA-positive at week 12 achieved significantly higher SVR rates when treated for 72 instead of 48 weeks (29% vs 17%, *P*=.040). However, this was seen primarily in patients who had measurable low viral loads at week 12 (<6,000 IU). They concluded that extended treatment is not warranted for genotype 1-infected patients who achieve an RVR or complete EVR, but is beneficial for patients with a partial EVR and low viremia levels at week 12.

In another study, Sanchez-Tapias and colleagues[10] treated 510 patients (all genotypes) with PegIFN-α2a plus ribavirin (800 mg/day). A total of 326 patients (291 genotype 1-infected) had detectable HCV RNA levels at week 4 and were then randomized to 48 or 72 total weeks

of treatment. Although the end-of-treatment response rate was similar between the groups, the SVR rate was higher in the 72 week group (45% vs. 32%; *P*=.01). For genotype 1-infected patients, the SVR rates were 28% and 44%, in the 48 and 72 week groups, respectively (*P*=.003). However, looking at the subanalysis in patients requiring extended therapy, this strategy was shown to be beneficial only in patients with a low baseline viral load (<800,000 IU/mL) (53% vs. 32% SVR), as opposed to those with high baseline viral loads (>800,000 IU/mL) (36% vs. 32% SVR).

Pearlman and colleagues[11] conducted a prospective trial in which 101 patients who achieved a partial EVR after 12 weeks of therapy with PegIFN-α2b and 800–1,400 mg/day of ribavirin were randomized to complete a total of 48 or 72 weeks of therapy. They found that, as with the other studies, there was no difference in end-of-treatment response between the two groups, but that SVR rates were significantly higher with extended treatment (38% vs. 18%; *P*=.026). They also noted that treatment extension did not seem to increase the rate of dose reduction or therapy discontinuation.

In the study by Mangia and colleagues mentioned previously, although extended therapy improved the rate of SVR in patients who achieved undetectable virus at week 12 (63.5% versus 38.1% with standard therapy), no partial EVR patient among those receiving standard 48-week therapy achieved SVR. Patients obtaining partial EVR and receiving 72 weeks of therapy achieved 7.5% (4/53) SVR. Overall, only 1.6% of all patients with a measurable level of virus at week 12 achieved SVR. However, 25% of patients withdrew from the study or were lost to follow-up.[7]

A limitation of many of the extended-duration trials conducted to date is the use of less-than-standard doses of ribavirin in one or more arms compared to US weight-based dosing. It is therefore difficult to ascertain whether the additional benefit is derived from extending the duration of therapy, or simply achieving required cumulative levels of ribavirin in the extended duration arms versus the standard arm.

Genotype 2 and 3 Patients

The standard of care for patients with genotype 2 and 3 infection is to treat with PegIFN plus ribavirin for 24 weeks. Recently, there has been interest in using RVR to predict those patients that can achieve viral eradication with an even shorter course. In a study by van Wagner and colleagues[12], 153 patients with genotype 2 or 3 infection were treated with PegIFN-α2a plus ribavirin 800–1200 mg/day. After 4 weeks, patients with an HCV RNA level below 600 IU/mL (n=142) were randomized to a total treatment duration of either 16 or 24 weeks. The end-of-treatment and SVR rates were 94% and 82% for the 16 week group, and 85% and

80% for the 24 week group, which were not statistically significant differences. The 11 patients in this study who did not achieve an RVR were treated for 24 weeks, with an SVR rate of only 36%. The authors concluded that patients with genotype 2 or 3 infection, with low baseline viral load and who achieve an RVR, could be effectively managed with a 16-week treatment duration. However, questions were raised as to how long to treat those patients not achieving an RVR.

Similarly, Dalgard and colleagues[13] compared the efficacy of 14 or 24 weeks of treatment with PegIFN-α2b plus ribavirin (800–1,400 mg/day) for patients with genotype 2 or 3 infection. A total of 122 patients were treated, and those who had undetectable HCV RNA levels at weeks 4 and 8 were assigned to 14 weeks of total treatment (n=95). The remaining patients (n=27) were treated for 24 total weeks. The SVR rate was 90% in the 14-week treatment group and 56% in the 24-week treatment group. Mangia and colleagues[14] then looked at 12 versus 24 weeks of treatment with PegIFN-α2b plus ribavirin (1,000–1,200 mg/day) in a similar population. A total of 283 patients were enrolled in their study. Of these, 70 were assigned to 24 weeks of treatment from the start (the standard duration group). For the remaining 213 (the variable duration group), those who achieved virus negativity at week 4 were assigned to 12 weeks of treatment (n=133) and those who did not received 24 weeks of treatment (n=80). The SVR rate was 76% for the standard duration group and 77% for the variable duration group (treated for 12 weeks or 24 weeks, based on RVR). The investigators noted that the shorter course of treatment was just as effective as the standard course for patients with genotype 2 or 3 infection who achieved an RVR. Further, they found that fewer patients in the variable-duration group receiving the 12-week regimen experienced adverse events and withdrew from the study than in the group receiving the 24-week regimen (P=.045).

In 2007, Shiffman and colleagues published the ACCELERATE study in the *New England Journal of Medicine*.[15] This study randomized 1,469 patients with genotype 2 or 3 infection to 16 or 24 weeks of treatment with PegIFN-α2a plus ribavirin (800 mg/day). The study was primarily designed to demonstrate non-inferiority of the 16-week regimen, but it failed to do so for the intent-to-treat population. The SVR rate was significantly lower in patients treated for 16 weeks than in patients treated for 24 weeks (62% vs. 70%; P<.001). Looking at patients who achieved an RVR, SVR rates were 79% in the 16-week group versus 85% in the 24-week group (P=.02). In those patients not achieving an RVR, SVR rates were 26% and 45%, respectively.

Taken together, these studies indicate that patients with genotype 2 or 3 infection and an RVR will achieve very good SVR rates with 12–16 weeks of treatment and may not need to continue for the standard 24-week duration. However, caution should be given to this approach as the relapse rate is likely to be somewhat higher and subsequently if patients can tolerate therapy for 24 weeks, this is still the ideal treatment duration. As with genotype 1 infection, there is interest in determining if a longer treatment duration of 48 weeks rather than 24 weeks may increase SVR rates among genotype 2 and 3 patients who do not achieve an RVR or complete EVR; further studies will clarify this issue.

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Utilizing Consensus Interferon in the Clinical Setting

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Hepatitis C therapy has progressed significantly since the IFNs were first introduced in 1990. The current standard-of-care for treatment is PegIFN in combination with ribavirin, given for 24–48 weeks, depending upon HCV genotype. SVR, of course, is the ultimate goal in treating hepatitis C, as the vast majority of patients who achieve an SVR do not show signs of viral recurrence and tend to show improvement in histologic disease even years later. The PegIFN/ribavirin combination is able to produce SVR rates of 50% in the general HCV-infected patient population. However, several patient subpopulations do not achieve the 50% SVR rate with PegIFN/ribavirin therapy. Generally, the best SVR rate that genotype 1 patient populations achieve is approximately 41%,[1] but among African-Americans with genotype 1 infection, the SVR rate is 26%. Another difficult-to-treat group is the nonresponders, or those who have failed previous PegIFN-based therapy. It seems that, for this group, retreatment with PegIFN/ribavirin provides no benefit, producing SVR rates of only 2–4%.[2] Lastly, HIV/HCV coinfected patients tend to have lower response rates, with SVR rates of only 27–40%.[3]

Classifying Patients by Response

As discussed previously, patients with an RVR achieve very high SVR rates—about 90%—when treated with PegIFN/ribavirin. Patients who achieve a complete EVR still do quite well, with SVR rates around 70%. Patients with a partial EVR can have SVR rates of 0–18%, and recent studies have suggested that prolonging therapy in this population can increase SVR rates to 7.5–38%.[4-7] Taken together, patients who achieve an RVR, a complete EVR, or a partial EVR comprise about two-thirds of all hepatitis C patients, and we can achieve SVR by using viral kinetics to plan duration of therapy and extend therapy where applicable.

This leaves several important groups, which are more challenging to treat. Partial responders experience a drop of at least 2 logs by week 12 or 24, but are still viral positive at that time. Most of these patients stop treatment because continuing treatment does not achieve negativity. Nonresponders represent a second group. However, there is some discrepancy among clinical trials regarding what constitutes nonresponse. In some studies, a null response has been defined as less than 1 log drop in HCV RNA, and in other studies it is less than a 2 log drop, but here we shall consider

any drop in HCV RNA of less than 2 logs by week 12 to be a nonresponse. A drop in HCV RNA of less than 0.5 log shall be considered a null response. Breakthrough patients are HCV RNA-negative at some point while on treatment, but during the course of therapy experience viral breakthrough. Although many of these patients are not adherent to therapy, others are adherent and experience breakthrough regardless. Once breakthrough occurs, these patients no longer respond to PegIFN/ribavirin. Finally, relapse patients are those who achieve an end-of-treatment response but then become HCV RNA positive after treatment is stopped.

Designating Candidates for Re-Treatment with Consensus Interferon

Consensus IFN has shown promising results in both the PegIFN/ribavirin nonresponder and relapse populations, with SVR rates of up to 37% for nonresponders and 69% for relapsers.

Two key studies have been conducted in the nonresponder population. The first was the DIRECT trial.[8] A total of 515 patients with a well-documented nonresponse to PegIFN/ribavirin were randomized to three arms initially (DIRECT 001) and treated with consensus IFN, either 15 µg daily or 9 µg daily, in combination with weight-based ribavirin. The third arm was a no-treatment arm, which later allowed patients to be randomized to either 9 µg or 15 µg of consensus IFN daily (DIRECT 002). The study was complicated in part by allowing dose adjustments based on hematologic changes. The protocol allowed reductions in the 15 µg group down to 9 µg, and in the 9 µg group down to 6 µg. Patients who developed anemia and a hemoglobin measure below 10 g/dL were required to reduce the ribavirin dose to 600 mg/day, which has since been found to negatively affect SVR rates. Growth factors were not allowed in the study. Another complication was that the patient population was extremely difficult to treat. Most of the patients were male, 20% were African-American, 95% were genotype 1, 90% had high viral load (>400,000 IU/mL), and most were overweight (mean weight = 90 kg; mean body mass index = 29.5). In addition, severe fibrosis (F3 or F4) was documented in approximately 60% of patients and steatosis was documented in 50% of the population. Thus, in the intent-to-treat (ITT) analysis, SVR rates were 6.9% and 10.7% for the 9 µg and 15 µg arms, respectively. However, partial responders (patients who had no cirrhosis

and who had a previous response of at least a 2 log drop in HCV RNA on treatment with PegIFN/ribavirin) actually achieved an SVR rate of 32%. In patients that maintained full dose of consensus IFN and ribavirin, SVR rates increased to 38%. Therefore, the DIRECT study, while demonstrating a respectable overall SVR rate of 11% in the 15 μg arm, clearly showed that there is a subgroup of partial-response patients who benefit even more significantly from therapy with consensus IFN.

Leevy and colleagues[9] very recently published a trial looking at the efficacy of consensus IFN for PegIFN nonresponders. They retrospectively identified 137 consecutive patients whose HCV RNA levels did not drop by at least 2 logs after 12 weeks of treatment with PegIFN-α2b plus ribavirin. These patients were then treated with consensus IFN 15 μg daily plus weight-based ribavirin for 48 weeks. If patients were HCV RNA negative after 12 weeks of consensus IFN treatment, the dose was reduced to 15 μg three times weekly for the remaining 36 weeks. They found that the overall SVR rate was 37%. In the subgroup of patients who were African American, the SVR rate was 27%. Interestingly, when patients who did not experience any reduction in HCV RNA levels on PegIFN/ribavirin (defined as less than a 0.5 log drop in HCV RNA by week 12) were treated with consensus IFN/ribavirin, no benefit was seen. The authors concluded that patients who have between a 0.5 log and a 2 log drop in HCV RNA after 12 weeks of treatment with PegIFN/ribavirin are good candidates for treatment with consensus IFN/ribavirin, and they can be expected to achieve SVR rates between 27% and 37%. On the other hand, patients with a null response (less than 0.5 log drop in HCV RNA) to PegIFN/ribavirin therapy by week 12 are less likely to achieve benefit from a switch to consensus IFN/ribavirin treatment.

Kaiser and colleagues presented data at Digestive Disease Week 2006 indicating that relapsers can achieve quite good SVR rates on consensus IFN.[10] A total of 120 patients (83% genotype 1) who had relapsed after 48 weeks of prior treatment with PegIFN/ribavirin were retreated with 72 weeks of either PegIFN-α2a or with consensus IFN 9 μg once daily. Both groups received concomitant weight-based ribavirin. The SVR rates were significantly higher in the consensus IFN arm compared with the pegylated interferon arm (69% vs. 42%; *P*<.05), showing that consensus IFN is a good choice for patients that relapse following initial HCV therapy.

Other Strategies for Retreatment

Of course, nonresponse has been a challenge for many years, and many strategies have been tried to successfully re-treat these patients. When PegIFN was introduced, there was great hope that it might be effective in producing a good SVR rate among patients who had failed therapy with conventional IFN plus ribavirin. This turned out not to be the case, because typical re-treatment SVR rates range from about 8% to 20%.[11,12] The REPEAT study,[13] a phase III, randomized, international trial, looked at the efficacy of 48 or 72 weeks of re-treatment with PegIFN-α2a plus ribavirin for patients who were nonresponders and relapsers to PegIFN-α2b plus ribavirin after at least 12 weeks of previous treatment. A total of 942 patients (537 with unknown quantitative response to previous therapy) were randomized to one of four treatment groups. Arms A and B received induction PegIFN-α2a 360 μg/week for 12 weeks, followed by 180 μg/week for a further 60 or 36 weeks, respectively, and arms C and D received PegIFN-α2a 180 μg/week for 72 or 48 weeks, respectively. All patients received concomitant ribavirin (1,000–1,200 mg/day). The investigators found that the most aggressive treatment, as seen in arm A, resulted in an SVR rate of only 16%. The SVR rates in arms B, C, and D were just 14%, 7%, and 9%, respectively.[14]

A number of differences between the REPEAT and DIRECT trials confound direct comparison of results. Prior response to PegIFN treatment was not well documented in the REPEAT trial. In addition, it was not known what proportion of patients in the REPEAT trial were required to have been treatment compliant on prior PegIFN/ribavirin therapy, whereas in the DIRECT trial, patients were documented 80/80/80 compliant to previous PegIFN/ribavirin therapy. There were also differences in the patient populations enrolled into the two trials. Patients enrolled in DIRECT had more advanced liver disease than those in REPEAT (60% vs 27% with stage F3–4 fibrosis) and DIRECT included a higher percentage of African American patients.

Other similar studies have found even lower response rates among nonresponders who were retreated with PegIFN/ribavirin, such as one by Afdhal and colleagues[15] that reported just a 3% SVR rate. Therefore, it is clear that PegIFN/ribavirin nonresponders receive little benefit from re-treatment with PegIFN/ribavirin, even with an aggressive course of induction therapy or longer duration of therapy.

Another agent that has been tested for the re-treatment of nonresponders is albumin IFN, a recombinant protein consisting of IFN-α2b genetically fused to the human albumin protein. Nelson and colleagues[16] randomized 115 patients with a previous nonresponse to PegIFN/ribavirin to receive one of 5 albumin IFN regimens (900 μg every 2 weeks, 1,200 μg every 2 weeks, 1,200 μg every 4 weeks, 1,500 μg every 2 weeks, and 1,800 μg every 2 weeks) in combination with weight-based ribavirin (1,000–1,200 mg/day). The treatment duration was 48 weeks, but the protocol was amended to allow extended treatment up to a total of 72 weeks for slow responders (patients who became HCV RNA negative after week 24). The overall SVR rate in this

study was 19%, and increasing albumin IFN dose or duration of treatment did not seem to affect response.

The experimental oral agent boceprevir has also been tested in combination with PegIFN plus ribavirin for non-responders to prior PegIFN therapy. Schiff and colleagues[17] enrolled 357 patients with genotype 1 HCV and a documented nonresponse to standard therapy (less than 2 log decrease in HCV RNA at week 12), and then randomized them to either PegIFN plus ribavirin (control) or to PegIFN/ribavirin plus boceprevir at different dosages. This trial had exclusion criteria that did not permit cirrhotic patients to be entered. The SVR rate in the control arm was 2%, which is similar to that seen in previous studies, and the SVR rates in the triple drug treatment arms ranged from 4% to 14%. From these data, it is clear that nonresponders with less than a 2 log decrease in HCV RNA on PegIFN/ribavirin are not good candidates for boceprevir. It should be noted that a similar group of patients did benefit from treatment with consensus IFN plus ribavirin, as seen in the Leevy and colleagues and DIRECT trials, with SVR rates between 27% and 38%.[8,9]

Consensus Interferon in Practice

We have seen that nonresponders benefit from consensus IFN/ribavirin treatment, as long as they have experienced a drop in HCV RNA of 0.5–2 logs on treatment with PegIFN/ribavirin. Nonresponders who experience a true null response of less than a 0.5 log drop in HCV RNA are less likely to respond to consensus IFN. Many nonresponder patients are highly motivated to achieve viral eradication and will commit to a strategy similar to that seen in the Leevy study. If a patient on PegIFN/ribavirin is not viral negative by week 12, consideration should be given to switching the patient to consensus IFN. For relapsers, there are multiple options. They can be re-treated with PegIFN/ribavirin; however, preliminary data suggest that treating with consensus IFN/ribavirin is more effective for this patient population. Further studies are ongoing and will clarify this issue.

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Notes