Clinical Roundtable Monograph

Gastroenterology & Hepatology October 2008

# The Future Use of Interferon in the Treatment of Hepatitis C: New Formulations, New Combinations

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**A CME Activity**
Approved for
1.0 *AMA PRA*
*Category 1*
*Credit(s)™*

**Release date:** October 2008
**Expiration date:** October 31, 2009
**Estimated time to complete activity:** 1 hour

## Abstract

Chronic hepatitis C viral infection is a major cause of liver disease, cirrhosis, and carcinoma. Current therapeutic approaches are aimed at achieving viral eradication and a sustained virologic response. To that end, the current standard of care for treatment of hepatitis C is pegylated interferon in combination with ribavirin. Although the mechanism behind interferon- and ribavirin-mediated therapy is not fully understood, both antiviral and immunomodulatory activities are believed to be at work. Despite continuing advances that have greatly improved the response to therapy, a significant percentage of patients will fail to clear the virus or must halt therapy due to serious adverse events. Current strategies to optimize interferon/ribavirin therapies include increasing the dosage or duration of therapy, as well as the use of early predictors of response to maximize treatment outcomes. In addition, novel therapies such as modified interferon agents and protease and polymerase inhibitors are being developed to improve efficacy in difficult-to-treat populations, as well as reduce the duration of treatment and treatment-related side effects.

Supported through an educational grant from
Novartis Pharmaceuticals Corporation and Human Genome Sciences, Inc.

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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 hepatitis C infection.

**Statement of Need/Program Overview:** Given that about half of all hepatitis C virus (HCV)-infected patients who receive treatment fail to achieve sustained virologic response, more effective therapies are clearly needed. Alternative therapies are also necessary for patients who are unable to tolerate standard HCV treatment. Dose modifications are required in 35–42% of treated patients due to poor tolerability, and about a third of these patients must ultimately discontinue treatment altogether. Early dose reductions or temporary interruptions compromise the chance of complete viral eradication. Peginterferon/ribavirin is contraindicated altogether in many patients with severe cytopenia, hepatic decompensation, renal insufficiency, poorly controlled autoimmune disease, severe cardiopulmonary disease, and active psychological problems. Fortunately, the field of HCV treatment is currently undergoing marked advances in the development of novel anti-HCV agents, and several emerging therapies have the potential to enhance the potent effects produced by peginterferon/ribavirin treatment. These include agents specifically targeted against HCV protease and polymerase enzymes as well as modified formulations of the interferon molecule.

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

1. Describe the treatment challenges in patients with chronic HCV undergoing standard treatment.
2. Enumerate the novel therapies currently in research to improve HCV treatment outcome.
3. Predict how new agents and combinations of agents may be used in the future to improve efficacy of HCV treatment.
4. Review how new agents and combinations of agents may be used in the future to improve patient adherence of HCV treatment.

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**John G. McHutchison, MD:** Dr. McHutchison discloses the following. Research grants: Abbott Laboratories, Anadys, Coley Pharmaceutical Group, DebioPharma, First Circle Medical, Inc., GlaxoSmithKline, Globe Immune, Gilead, Human Genome Sciences, Idenix Pharmaceuticals, Intarcia, Medtronic, Inc., Novartis Pharmaceuticals, Pfizer, Inc., Pharmasset, Roche Pharmaceuticals, Salix Pharmaceuticals, Sanofi-Aventis, Schering-Plough, Valeant Pharmaceuticals, Vertex Pharmaceuticals, Virochem, Wyeth Pharmaceuticals. Consulting fees: Abbott Laboratories, Ambrx, Anadys, Biolex, Cerus, Coley Pharmaceutical Group, DebioPharma, Epiphany Biosciences, First Circle Medical, Inc., GlaxoSmithKline, Gilead, Human Genome Sciences, Idenix Pharmaceuticals, Idera, Implicit, Intarcia, InterMune Pharmaceuticals, National Genetics Institute, Novartis Pharmaceuticals, Peregrine, Pfizer, Inc., Pharmasset, Roche Pharmaceuticals, Schering-Plough, United Therapeutics, Valeant Pharmaceuticals, Vertex Pharmaceuticals, Virochem, Wyeth Pharmaceuticals.

**Mark Sulkowski, MD:** Dr. Sulkowski discloses the following. Consulting fees: Boehringer Ingelheim Pharmaceuticals, Inc., Gilead Sciences, Human Genome Sciences, Merck & Co., Roche Pharma, Schering-Plough.

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# Understanding the Interferon Molecule

Ira M. Jacobson, MD

Interferons (IFNs) are naturally occurring glycoproteins produced by a variety of cell types in response to stimuli such as infectious agents.[1,2] There are three classes of interferons: type I, type II (IFN-γ), and type III (type I-like interferons). Type I interferons include, among others, the alpha interferons (IFN-α) of which there are at least 13 subtypes that are closely related, but not identical. The effectiveness of IFN-α in the treatment of hepatitis C virus (HCV) is attributable to potent antiviral and immunomodulatory properties, but significant adverse events and patient subpopulations with poor therapeutic responses detract from its overall usefulness.

## The Mechanism of Action of Interferon-α Against Hepatitis C

When patients are exposed to exogenous IFN-α, the net effect is a cascade of events that begins with the binding of IFN-α to the IFNAR-1 and IFNAR-2 receptor complex on the surface of a cell. Binding the receptor activates the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway, which ultimately leads to the activation of hundreds of interferon-stimulated genes (ISGs).[3] The JAK family members, tyrosine kinase 2 (TYK2) and JAK1, are activated through tyrosine phosphorylation, which in turn phosphorylates the STATs. The activated STATs dimerize and translocate to the nucleus where they induce the expression of ISGs. Interestingly, type I interferons are able to induce all 7 members of the STAT family, with STATs differentially activated according to the cell type. In fact, IFN-α was shown to induce STATs 1, 2,3, and 5 in primary human hepatocytes, which resulted in the dramatic upregulation of 44 genes involved in antiviral, tumor suppressor, and proapoptotic pathways.[4] The potent transcription factor IFN-stimulated gene factor 3 (ISGF3), which consists of STAT1, STAT2, and unphosphorylated IFN regulatory factor 9 (IRF-9), binds IFN-stimulated response elements in the promoters of ISGs, thus inducing their transcription.[2,3] The activation of the ISGs leads to the production of a multitude of proteins that mediate a complex array of biologic effects.

In the field of hepatitis C, it remains unclear which of the many interferon-stimulated gene products are most responsible for the therapeutic effect. IFN-α is not an HCV-specific therapy, but rather a nonspecific antiviral agent that inhibits viral replication, reduces the infection of cells, and induces death in virally infected cells.[1] There are a number of mechanisms by which IFN-α is believed to mediate its antiviral effects. These effects include, but are not limited to, the induction of 2'-5' oligoadenylate synthetase (2'-5' OAS), PKR, and myxovirus (Mx) proteins.[2] 2'-5' OAS protects cells from viral infections through the production of 2'-5' oligoadenylate (2-5A), which activates RNAse L endonuclease to degrade viral and cellular RNA.[5] PKR, a serine-threonine kinase, is activated by intracellular double-stranded RNAs.[6] Activated PKR phosphorylates eukaryotic translation initiation factor 2 alpha (eIF2α), which leads to a general block of translation. PKR can also modulate transcription through IRF factors and STATs.[2] Lastly, MxA accumulates in the cytoplasm of IFN-treated cells, which blocks the transport of viral components.[7]

In addition to its antiviral effects, IFN-α also has immune-modulating properties.[1] IFN-α stimulates the immune system by activating immune cells such as macrophages, natural killer cells, and cytotoxic T cells. The class I major histocompatibility complex (MHC I), which is important for displaying viral antigens to the immune system, is upregulated. IFN-α may also induce antibody production by B cells, upregulate cytokine and chemokine production, and induce costimulatory molecules necessary for proper activation of T cells.

Although IFN-α has a well documented antiviral effect, there remains much debate about how IFN-α is actually working in patients with HCV. A two-phase viral decline is observed in HCV patients treated with IFN-α.[8,9] The steep phase-1 decline is mediated by an IFN-α–mediated block on viral replication. The second, more gradual, phase-2 decline ultimately determines what happens to the patient clinically and has been attributed to an immune-mediated clearance of infected cells. It is important to note that interferon therapy does not specifically target HCV and relative roles of the antiviral versus immune modulatory properties of interferon that mediate its therapeutic action in chronic hepatitis C remain unclear.

## The Role of Pegylation in Improving the Efficacy of Interferon Therapy

Interferon alfa was first administered as a monotherapy (3 million units 3 times/week [TIW]) in 1990. The advent of virologic testing in the early 1990s brought to light a meager sustained virologic response (SVR) of only 6–12%. Subsequently, the standard duration of therapy for chronic HCV was increased from 24 weeks to 48 weeks, which resulted in SVR rates of 12–19%.[1,10,11]

In an effort to improve the antiviral activity of IFN-α, a consensus interferon was developed in the mid-to-late 1990s. This novel synthetic IFN-α consists of the most commonly observed amino acids from several IFN-α nonallelic subtypes.[12] In vitro evidence suggested that the consensus interferon has greater potency than traditional IFN.[12,13] However, the SVR rates in treatment-naïve patients when consensus interferon was given as monotherapy were comparable to IFN-α2b.[14] With the addition of ribavirin in 1998, which was only available initially in combination therapy with IFN-α2b, consensus interferon became used less frequently.

The unfavorable pharmacokinetics of standard interferon, with its half-life of four hours, combined with its clinical limitations, led to the development of pegylated interferon (PEG IFN). Pegylation is the covalent binding of a linear or branched polyethylene glycol molecule to the IFN molecule. The addition of PEG molecules prolongs the plasma half-life of the drug, reduces the rate of clearance, and reduces immunogenicity.[10,11,15,16] The size of the PEG molecule influences the PK half-life and biologic activity of the interferon molecule. Specifically, a larger PEG molecule will have a greater loss in activity, but a more protracted serum half-life.

PEG IFN-α was developed in an effort to reduce the frequency of administration to once weekly. Two commercially available PEG IFNs were introduced in the early 2000s: PEG IFN-α2b (12 kilodaltons) and PEG IFN-α2a (40 kilodaltons). Both formulations are given once weekly, thereby enhancing the convenience of the regimen. The response rate of both PEG IFNs remains strongly genotype-dependent (genotype 1 SVR rates: 14% and 28%; genotypes 2 /3 SVR rates: 49% and 39%; PEG IFN-α2b and PEG IFN-α2a, respectively, when dosed as monotherapy).[10,11]

There has been much discussion over the years regarding the implications of PEG size and the outcomes of therapy. PEG IFN-α2a is formulated as a fixed dose product, whereas PEG IFN-α2b is always formulated as a weight-based product. The only large, randomized trial to compare the two PEG formulations head-to-head is the IDEAL study.[17,18] This study enrolled approximately 3,000 treatment-naïve US genotype 1 patients with chronic HCV to determine the safety and efficacy of weight-based ribavirin dosing (800–1,400 µg/day) and PEG IFN-α2b dosing (arm 1: PEG IFN-α2b 1.5 µg/kg/week; arm 2: PEG IFN-α2b 1 µg/kg/week). The study also included a third arm with PEG IFN-α2a (arm 3: PEG IFN-α2a 180 µg/week plus 1,000–1,200 mg/day ribavirin). The SVR rates were statistically the same across all groups (PEG IFN-α2a: 41%, higher-dose PEG IFN-α2b: 40%, and lower-dose PEG IFN-α2b: 38%). The end of treatment response rate was higher with PEG IFN-α2a (64% vs 53% and 49%), but the relapse rate was also higher, which led to the equivalent SVR rates.

## Adverse Effects and Challenges of Long-term Use

Administration of interferon is associated with a number of toxicities that lead to discontinuation rates of approximately 10%, and a number of patients require dose reductions.[1,19] Flu-like symptoms occur in approximately 85% of patients with the initial administration of interferon.[19] These symptoms improve over time and can be offset by premedication with nonsteroidal anti-inflammatory drugs or acetaminophen.

Neuropsychiatric effects include chronic fatigue, cognitive impairment, headaches, insomnia, depression, and peripheral nephropathy. In fact, as many as 20–30% of patients may be at risk for depression during therapy and should be treated with antidepressants as needed.[19,20] Pulmonary side effects can range from a dry cough to dyspnea, and more seriously but rarely, interstitial pneumonitis. Asthenia, alopecia, dyspepsia, altered vision, and impaired hearing may also occur. Retinopathy may occur and can be asymptomatic or result in symptoms such as "floaters." Also important, but uncommon, is the hearing impairment that may develop from unilateral or bilateral sensorineural hearing loss.

There is also a risk of bone marrow suppression resulting in cytopenias such as neutropenia, thrombocytopenia, and anemia. The latter compounds the hemolytic anemia that ribavirin causes by impairing compensatory bone marrow production. In the case of neutropenia, dose reductions are recommended. Erythropoietin has been used to augment hemoglobin levels, minimize ribavirin dose reductions, and improves quality of life[21] but has never been demonstrated to increase SVR rates and remains unapproved for this indication. Short-term courses of granulocyte colony-stimulating factor may be administered in cases of severe neutropenia,[20] but, like erythropoietin, is unapproved for this indication.

The administration of IFN can also aggravate or induce underlying autoimmune inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, psoriasis, sarcoidosis, colitis, or pancreatitis. Autoimmune diseases are considered strong contraindications for IFN therapy. In addition, autoimmune thyroid disease occurs in about 5% of patients and leads to permanent hypothyroidism in a smaller number.

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# Current Strategies in the Optimization of Interferon-based Combination Therapies

Mark Sulkowski, MD

## Rationale and Mechanism of Combination Therapy with Ribavirin

Although pegylation of interferon alfa (PEG IFN) prompted a 10% increase in SVR rates for genotype 1 HCV patients,[1,2] addition of ribavirin (RBV) to interferon alfa led to the most significant increase in viral response rates for patients infected with hepatitis C, particularly those with genotype 1 infection. Prior to the introduction of RBV, IFN monotherapy conferred an SVR in approximately 8% of genotype 1 and 24% of genotype 2/3 treatment-naïve patients.[3] The addition of RBV more than doubled the SVR rate,[3,4] with the highest SVR rates observed when patients are treated with PEG-IFN/RBV (genotype 1: 42% to 46%, genotype 2/3: 80%).[5,6]

Even though the initial study of RBV occurred more than 10 years ago,[7,8] it remains unclear how RBV exerts an antiviral effect. There are four major proposed mechanisms for RBV activity, some of which have now been refuted. RBV does appear to have significant immune-modulating activity.[9,10] RBV enhances the production of Th1 and proinflammatory cytokines (IFN-γ,TNF-α), and suppresses Th2 cytokines (IL-4, IL-5).[11] The net effect of this skewing is to enhance the ongoing proinflammatory and cytotoxic response to the virus, thereby working synergistically with the activity of IFN-α. RBV has also been shown to inhibit inosine monophosphate dehydrogenase (IMPDH), leading to a block in viral replication.[9,10] However, studies using other IMPDH inhibitors suggest that the IMPDH pathway is not a central mechanism involved in RBV activity.[9,10] RBV may also act directly on the RNA polymerase, although the data for this direct antiviral effect is lacking. Given the weak inhibition of RNA polymerase, and the limited effectiveness of RBV monotherapy in vivo, the direct antiviral effect on HCV does not appear to be the primary mechanism by which RBV inhibits HCV.[9] Finally, it has been proposed that RBV creates lethal RNA mutagenesis.[10] By acting as a viral mutagen, RBV may increase the mutation rate of the virus leading to a reduction in the overall infectivity of the virus. Although the definitive mechanism of action remains to de identified, RBV remains a critical and effective agent in the treatment of HCV.

## Strategies to Maximize SVR

There are a number of factors that influence viral response rates to PEG IFN/RBV therapy. Some of these are fixed, meaning that the patient or the treating physician cannot modify them. These factors include race, HCV genotype, HCV RNA level (ie, viral load), and liver fibrosis. It is well documented that African Americans have a lower response rate compared to Caucasians. This response differential is quite large, as genotype-1 infected African-American patients have SVR rates of 23–26%, compared to SVR rates of approximately 44% for Caucasian patients.[12] HCV genotype is another important factor that impacts treatment outcome. Against genotypes 2 and 3, treatment with PEG IFN plus low-dose RBV (800 mg daily) for 24 weeks yields response rates of approximately 70–80%.[13] In contrast, treatment of genotype-1 patients with PEG-IFN plus low-dose RBV for 24 weeks results in an SVR rate of only 29%. This can increase to between 40% and 50% when standard, weight-based doses of RBV are used (1,000-1,200 mg/day) in conjunction with a longer duration of treatment.[13] Among those infected with genotype 1, one of the strongest predictors of response is baseline hepatitis C viral load. Genotype 1 patients with baseline hepatitis C viral loads of more than 600,000 IU/mL are less likely respond to PEG IFN/RBV than those with low viral loads.[12] The final fixed factor that does not respond well to PEG-IFN/RBV is significant fibrosis. Individuals with stage 3 or 4 fibrosis on the METAVIR scoring system have SVR rates that range from 21–24% with the standard PEG IFN/RBV regimen, compared to rates of 42–44% for patients with stage 0,1, or 2 fibrosis.[12]

From a clinical perspective, it is important to focus on those factors that may be modified. Metabolic syndrome has emerged as a potent factor in patient responsiveness. Several studies examining insulin resistance using the insulin resistance index (HOMA-IR), found that those patients with a higher HOMA-IR responded less well to therapy.[14-16] In addition, an elevated fasting glucose level greater than 100 (impaired glucose tolerance) is associated with a 10% to 15% lower SVR after PEG IFN/RBV treatment.[17] This observation suggests that clinicians should attempt to modify insulin resistance and glucose intolerance prior to HCV therapy in an effort to improve SVR rates. While definitive studies are lacking, weight loss, exercise and, in some patient pharmacologic therapy with agent to improve insulin sensitivity may be considered in HCV-infected patients with documented insulin resistance.

A second modifiable factor is PEG IFN/RBV dose and duration of treatment. An intriguing study by Fried and colleagues[18] looked at management of patients with genotype 1 infection, who had body weight greater than 85 kg and high viral load (>800,000 IU/mL). These "hard-to-treat" patients received PEG IFN at 180 (standard dose) or 270 (high dose) µg/week plus RBV at 1,200 (standard dose) or 1,600 (high dose) mg/day. While the study was relatively small (188 patients randomized to four treatment groups), the highest SVR rate was observed when higher doses of PEG IFN and RBV were used compared to standard doses of each agent (28% vs 47% ). The role of RBV and adequate dosing was also highlighted in the WIN-R study by Jacobson and colleagues.[19] This study examined PEG-IFN plus either weight-based dosing (800–1,400 mg/day) or a fixed dosing (800 mg/day) of RBV. The most difficult to treat patients, genotype 1 infected African Americans, benefited from higher dose RBV. This data suggests that a critical issue in maximizing SVR is to deliver an adequate RBV dose of greater than 13 mg/kg/day.

Viral kinetics during HCV therapy is also an important tool to maximize response to PEG IFN/RBV. Viral response metrics during therapy can be divided into 3 categories: rapid virologic response (RVR) defined as undetectable HCV RNA at week 4, complete early virologic response (EVR) defined as undetectable HCV RNA at week 12, or partial EVR defined as a still detectable, but greater than 2 log drop, in HCV RNA at week 12. Patients with partial EVR who obtain HCV RNA undetectability by week 24 of therapy are consider by many experts to be late or "slow" responders.[20] Across a number of different studies, RVR is consistently associated with an SVR rate of around 85–90%.[21,22] Patients who develop a complete EVR have a reasonable probability of achieving SVR.[22,23] For genotype 2 and 3 patients, RVR is a better predictor of SVR than EVR, because EVR is achieved in greater than 90% of these patients, whereas RVR is observed in 67%.[24] In some settings, patients who achieve RVR may benefit from a shortened treatment course; however, the risk of viral relapse may be higher with truncated treatment and patients should be carefully evaluated before stopping therapy.[20,24] Conversely, genotype 2 or 3 patients who do not achieve RVR or genotype 1 patients who achieve only a partial EVR may benefit from longer therapy and higher drug doses.[20,24]

Over the last several years, it has been suggested that extending therapy to 72 weeks for genotype 1-infected slow virologic responders may be associated with higher rates of SVR. In the TERAVIC 4 study,[25] slow responders (defined as HCV RNA detectable at treatment week 4) were randomized to receive either 48 weeks or 72 weeks of therapy. The end-of-treatment response rates were similar in the 72-week and 48-week groups (61%). The SVR rate was only 32% in the 48-week treatment group versus 45% in the 72-week treatment group. The primary difference was in the rate of virologic relapse (48% vs 26%; 48-week and 72-week, respectively). In a second study by Pearlman and colleagues,[26] individuals who failed to achieve complete EVR received either 72 weeks of therapy or 48 weeks of therapy. The end-of-treatment response was very similar, 45% and 48%, but the SVR

rates were significantly different (18% vs 38%; 48 weeks and 72 weeks, respectively). The relapse rate was higher in the 48-week treatment group versus the 72-week treatment group (59% vs 20%). These studies, among others, suggest that an individual patient's viral kinetics may be useful in determining optimal treatment duration.

## Options for Re-treatment

The previous dosage of PEG IFN/RBV, the use of standard IFN versus PEG IFN, the duration of therapy, adherence, and interfering factors (on-treatment depression or ongoing drug or alcohol use) should all be considered when evaluating a prior nonresponder for re-treatment. Options for re-treatment include higher doses of PEG IFN and/or RBV, re-treatment with longer durations of PEG IFN/RBV, or consensus IFN/RBV. Recent studies are providing further insight into the optimal approaches for re-treatment.

The REPEAT trial[27] studied 942 patients treated with PEG IFN/RBV, who were then retreated with PEG IFN-α2a/RBV. Patients were divided into four treatment groups that all received 1,000-1,200 mg/day RBV: two groups received standard-dose PEG IFN/RBV for 48 or 72 weeks and two groups received a 12-week high-dose induction of PEG IFN (360 µg once weekly) followed by 60 or 36 weeks of standard-dose PEG/IFN. Induction dosing was ineffective and provided no additional benefit to the response rate. However, those who received longer therapy, had a 14–16% response rate versus 7–9% on the standard duration. Overall, re-treatment of a patient with PEG IFN/RBV results in a relatively low response rate, but longer treatment may provide some benefit to patients who achieve an undetectable HCV RNA during re-treatment. The EPIC3 trial[28] studied nonresponders to both standard IFN/RBV and PEG IFN/RBV who were retreated with PEG IFN-α2b/RBV. The overall response was 14% for nonresponders, very similar to that seen in the REPEAT trial. It is important to note that in this study, patients who achieved a negative viral load (relapsers), had a higher SVR rate of 39%. In the DIRECT trial,[29] 343 nonresponders were randomly assigned to receive consensus IFN (either 9 µg/day or 15 µg/day) plus standard RBV for 48 weeks. The response rates were comparable to the PEG IFN/RBV re-treatment studies, with an SVR rate of 5% for the low-dose consensus IFN group and 10% for the high-dose consensus IFN group.

These studies suggest that re-treatment of a patient who was a prior nonresponder to PEG IFN/RBV, the anticipated response rate will be between 10–15%, whether you use PEG IFN-α2a/RBV, PEG-IFN-α2b/RBV, or consensus interferon/RBV. It should be noted that the re-treatment response rates are better among relapsers; however, less data is available to guide decisions on the type and duration of re-treatment.

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# Novel Agents and Emerging Strategies to Optimize Outcomes

John G. McHutchison, MD

## Albuferon

An emerging strategy for the treatment of patients with chronic HCV infection is the optimization of the interferon component of our current therapies. One such compound is albuferon, which is human serum albumin genetically fused to the standard non-pegylated IFN-α2b molecule.[1] The long half-life of albumin allows for reduced dosing frequency.[1] Results from phase II trials of treatment-naïve genotype 1 patients[2] and genotype 2/3 patients[3] indicate that albuferon can be administered subcutaneously every 2 weeks (q2wk) or every 4 weeks (q4wk) and deliver significant antiviral activity with efficacy comparable to once-weekly PEG IFN formulations. In the genotype 2/3 study, patients received RBV plus 1,500 µg of albuferon (q2wk or q4wk) for 24 weeks. The SVR rates were 77.3% (q4wk) and 61.9% (q2wk). In the genotype-1 study, patients received PEG IFN-α2a/RBV; 900 µg albuferon q2wk plus RBV; or 1,200 µg albuferon (q2wk or q4wk) plus RBV. The SVR rates ranged from 50% to 58% for all treatment groups. In both studies, the highest discontinuation rates due to adverse events occurred in the high dose q2wk albuferon arms, with the most frequent adverse event reported as headaches. Additional phase II data suggest that treatment with albuferon every 2 weeks may lead to appreciable differences in quality-of-life issues, in addition to a more convenient dosing schedule. Therefore, the potential advantage of using albuferon is increased convenience and adherence, which in turn may theoretically enhance efficacy.

Phase III trials of albuferon in both genotype-1 and genotype-2/3 patients are currently in progress.[4,5] The goal of these trials is to compare safety, efficacy, and health-related quality-of-life issues of albuferon/RBV to PEG IFN-α2a/RBV and demonstrate noninferiority. If albuferon is approved from a regulatory standpoint, it will provide an alternate form of interferon that can potentially improve convenience and/or safety for patients with chronic HCV infection. In addition, there remains the possibility that albuferon could be used in combination with other novel direct antivirals, such as the protease or polymerase inhibitors. While these studies have not yet been conducted, more elaborate regimens of protease and/or polymerase inhibitors combined with IFN and RBV will hopefully lead to enhanced efficacy.

## Other Novel IFNs in Development

There are many other alternate IFN preparations currently in development. Several controlled-release formulations are currently being investigated, including encapsulation of PEG-IFN or IFN in liposomes,[6] vesicles,[7] extended duration delivery devices,[8] and colloidal suspensions of nanoparticles.[9] Recently, a phase I trial of a controlled-release preparation of nonpegylated IFN-α2b, was completed and found to be effective for dosing once every two weeks.[10] Oral and inhaled formulations are also being developed, in addition to other type I and III IFNs.[11-13] Although novel IFN therapies are in various stages of clinical and preclinical development, their premise is the same: to develop an IFN that can be used in conjunction with RBV and newer direct antivirals with an improved pharmacokinetic profile that will be more tolerable and allow for less frequent dosing.

## Protease and Polymerase inhibitors

The most exciting and furthest developed novel agents currently in this field are drugs targeting enzymes of the HCV replication complex. There are a number of studies with agents targeting either the HCV-specific protease or polymerase in clinical phase I-III trial development. The two most advanced agents, telaprevir and boceprevir, are both NS3/4A serine protease inhibitors.[14]

### *Telaprevir*

Data from phase II trials of telaprevir in combination with PEG-IFN/RBV was recently presented at the 43rd annual meeting of the European Association for the Study of the Liver (EASL).[15,16] In the PROVE1 study,[16] treatment-naïve genotype-1 infected HCV patients were randomly assigned to receive 750 mg telaprevir every 8 hours plus PEG IFNα2a/RBV for 12 weeks, telaprevir plus PEG IFNα2a/RBV for 12 weeks followed by PEG IFNα2a/RBV for 12 weeks, telaprevir plus PEG IFNα2a/RBV for 12 weeks followed by PEG IFNα2a/RBV for 36 weeks, or standard PEG IFNα2a/RBV for 48 weeks. This study found that patients who received telaprevir were more likely to achieve RVR (79% vs 11%) and EVR (70% vs 39%) than patients who received standard therapy. In addition, the SVR rate was 61% in the 24-week telaprevir arm versus 41% in the standard therapy arm, demonstrating that the length of therapy can be effectively shortened to 24 weeks. After treatment, the proportion of individual patients who achieved RVR and who subsequently relapsed was very low (2%) in the 24-week telaprevir combination therapy group. The PROVE2 study[15] found similar results. In addition, this study also found that telaprevir/PEG IFN combination therapy without RBV increased the likelihood of relapse and decreased the proportion of patients who achieved undetectable levels of HCV RNA. By treating genotype 1 patients with telaprevir for 12 weeks in combination with PEG IFN/RBV, with an additional PEG IFN/RBV follow-up, the number of patients who achieve RVR and SVR was significantly increased with a very low relapse rate. Phase III clinical trials of telaprevir for genotype 1-infected treatment-naïve patients[17] and genotype 1 patients who failed to achieve a sustained response with prior PEG IFN/RBV therapy[18] are currently underway.

As expected, there are several potential drawbacks associated with treating patients with protease inhibitors and new classes of direct antiviral drugs in general. Virologic breakthroughs occur, with treatment resistance and emergent viruses occurring in approximately 2–7% of patients.[19] However, suppression of these resistant strains has been documented to occur with subsequent PEG IFN/RBV combination therapy. Discontinuations were also more common with telaprevir than standard therapy. Rash associated with this protease inhibitor was responsible for approximately half of the discontinuations. Also, it appears that anemia may be exacerbated when telaprevir is given in combination with RBV. However, when telaprevir is stopped as determined by the study protocols, hemoglobin levels return to the values observed with RBV. Although the duration of therapy can be shortened and more patients can achieve SVR with telaprevir combination therapy, there are also more discontinuations, a different side effect profile, and some virologic breakthroughs. The long-term consequences of breakthrough are unclear at the current time, but the enhanced sustained response rates with truncated duration of therapy represents an exciting step forward in HCV therapy.

### *Boceprevir*

Interim data from the SPRINT-1 trial of boceprevir was also recently presented at EASL.[20] In the SPRINT-1 trial, treatment-naïve genotype-1 infected patients were randomly assigned to four treatment groups: 4 weeks of PEG IFN/RBV followed by 24 or 44 weeks of 800 mg twice-daily boceprevir plus PEG IFN/RBV (lead-in arm), boceprevir plus PEG IFN/RBV for 28 or 48 weeks (no lead-in arm), boceprevir plus PEG IFN and low-dose RBV for 48 weeks, and standard PEG IFN/RBV for 48 weeks. Week 4 response rates were highest for those patients in the lead-in arm (62%) versus the no lead-in arm (38%) or standard therapy arm (8%). Week 12 response rates were 79%, 69%, and 34% (respectively). Interim 12-week SVR rates in the 28-week arms were comparable (57% in the lead-in arm vs 55% the in no lead-in arm). Recently released data from the 48-week treatment arm demonstrates high 12-week SVR rates for those patients in the lead-in arm (74%) verses the standard 48-week therapy arm (38%).[21] Although these data are preliminary, it appears that boceprevir, like telaprevir, can lead to higher SVR rates in difficult-to-treat genotype 1 patients. Phase III trials of boceprevir in combination with PEG IFN/RBV for the treatment of genotype-1 infected patients who failed prior PEG IFN/RBV therapy (RESPOND-2)[22] and treatment-naïve genotype 1 patients (SPRINT-2)[23] are currently underway.

Boceprevir therapy is, however, also associated with drawbacks. The emergence of drug resistant viral variants has been observed with boceprevir monotherapy.[24] However, when lead-in therapy is used, the rate of viral breakthroughs is reduced, but not abolished (4% in lead-in vs 8% in non lead-in regimen).[20] Discontinuation rates due to adverse events are also higher in the boceprevir groups (11% in lead-in and 15% in non lead-in) as compared to the standard therapy (8%). The primary adverse events associated with discontinuation were fatigue, nausea, headache, and anemia. In the boceprevir arm with low-dose RBV, adverse-event discontinuations were reduced (8%) but viral breakthrough was greater (19%).

### *Outstanding Issues in the Treatment of HCV With Protease Inhibitors*

There are several outstanding issues regarding the use of protease inhibitors for the treatment of chronic HCV. The total duration of therapy, the length of exposure to the protease inhibitor, side effects, and the emergence of resistant strains are all key issues that must be resolved. Another important issue is the "lead-in" concept. It is believed that this approach may theoretically decrease viral load prior to the introduc-

tion of a specific protease inhibitor. This may, in theory, limit the early emergence of protease-inhibitor–resistant viruses. The evidence is limited, but this important concept will need to be proved or disproved in the near future as ongoing clinical trials are completed. It should also be noted that while the protease inhibitor class of drugs are potent inhibitors of viral replication, with profound reductions in serum HCV RNA in days, they do have short half lives that require frequent dosing.[25] Boceprevir is administered twice daily and telaprevir is administered three times daily, which may present issues in terms of patient adherence to the prescribed regimen. More research is critically needed to evaluate the impact of adherence on virologic resistance and clinical breakthrough.

Recent studies also suggest that when patients are exposed to a protease inhibitor, they can develop both low-level and high-level treatment resistant variants.[19,26] Those variants are much less sensitive to the drug in question. When these patients are followed over time, there is a reversion to the original nonresistant form of the virus over a period of 3–7 months following cessation of the protease inhibitor.[18] Further studies are needed to clarify the long term clinical effects of harboring these variants, and what will transpire when these patients are re-exposed to another protease inhibitor or drug of the same class. It is unclear if these patients will quickly develop resistance, whether they can be effectively treated with either another additional course of therapy including a protease or a polymerase inhibitor, or if their disease has been altered in such a way that their ability to respond will be affected in the future. All these issues must be carefully and critically addressed in the near term.

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# CME Post-Test: The Future Use of Interferon in the Treatment of Hepatitis C: New Formulations, New Combinations

*Circle the correct answer for each question below.*

1. Increasing the duration of IFN monotherapy from 24 weeks to 48 weeks resulted in a sustained virologic response in what proportion of patients?

   a. 6–12%  b. 12–19%  c. 24–36%  d. 38–42%

2. According to the IDEAL study, what was the approximate SVR rate for genotype-1 patients treated with either formulation of PEG-IFN?

   a. 20%  b. 40%  c. 60%  d. 80%

3. What is the most common side effect associated with IFN treatment?

   a. Flu-like symptoms  b. Depression
   c. Autoimmune disease  d. Retinopathy

4. Which two mechanisms mostly likely play a central role in ribavirin activity?

   a. Immunomodulation and RNA mutagenesis
   b. Inhibition of IMPDH and RNA polymerase
   c. Both of the above
   d. None of the above

5. According to the TERAVIC 4 study, extending the duration of treatment to _____ weeks for slow responders increases the SVR rate and decreases the relapse rate.

   a. 48  b. 60  c. 72  d. 96

6. The REPEAT trial found that induction dosing was effective in increasing response rates.

   a. True  b. False

7. According to the DIRECT trial, re-treatment of nonresponders with high-dose consensus interferon resulted in what SVR rate?

   a. 5%  b. 10%  c. 15%  d. 20%

8. Treatment with albuferon may result in which of the following?

   a. More convenient dosing schedule
   b. Improved patient adherence
   c. Improved quality of life
   d. All of the above

9. In the PROVE1 study, how did the SVR rate of the 24-week telaprevir arm compare to standard therapy?

   a. SVR rate was higher in the 24-week telaprevir arm
   b. SVR rate was higher in the standard therapy arm
   c. SVR rate was similar in both arms

10. Which of the following is NOT associated with the use of protease inhibitors for HCV treatment?

    a. Elevated discontinuation rates
    b. Frequent dosing
    c. Poor viral load reduction
    d. Generation of treatment-resistant variants

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## Evaluation Form *Please answer the questions that follow.*

**What is your practice type?** (Please check one box.) ✹ MD/DO ✹ PA/Nurse Practitioner ✹ RN ✹ Other _____

**What is your area of specialization?** ✹ Gastroenterology ✹ Hepatology ✹ Internal Medicine
✹ Infectious Disease ✹ Family Practice ✹ Other _____

**What is the setting for your practice?**
✹ Solo practice ✹ Single specialty Group Practice ✹ Multi-specialty Group Practice ✹ Government
✹ Managed care health system ✹ University/teaching system ✹ Hospital ✹ Resident/Fellow ✹ Other _____

**Approximately how many patients with chronic HCV does your practice manage?** ✹ <10 ✹ 10–25 ✹ 26–50 ✹ >50

**How many years have you been in practice?** ✹ <5 ✹ 5–10 ✹ 11–20 ✹ >20

**To what extent do you agree with the following statements?** (Please circle the appropriate number on the scale.)
1 = Strongly Disagree 2 = Disagree 3 = Somewhat Disagree 4 = Somewhat Agree 5 = Agree 6 = Strongly Agree

- Patients with chronic hepatitis C viral (HCV) infection and comorbid metabolic syndrome generally will achieve better sustained viral response (SVR) rates on pegylated interferon/ribavirin (PEG IFN/RBV) therapy if steps are taken to lower insulin resistance prior to initiating therapy.

  *Strongly Disagree 1 2 3 4 5 6 Strongly Agree*

- A patient with genotype 2 HCV who achieves rapid viral response (RVR) on PEG IFN/RBV therapy has a higher probability of achieving SVR than a genotype 2 patient who achieves early viral response (EVR) on the same therapy.

  *Strongly Disagree 1 2 3 4 5 6 Strongly Agree*

- Preliminary clinical trail data indicate that the longer half lives of novel interferon agents in development permit less frequent dosing schedules (q 2 to 4 weeks).

  *Strongly Disagree 1 2 3 4 5 6 Strongly Agree*

- Preliminary clinical trial data indicate that protease inhibitors are active in treating the more resistant genotype 1 form of HCV, producing higher SVR rates than standard therapy.

  *Strongly Disagree 1 2 3 4 5 6 Strongly Agree*

- Emergence of resistant strains and viral breakthrough are known challenges of protease inhibitor therapy for HCV, although the long term clinical significance of either has not been assessed.

  *Strongly Disagree 1 2 3 4 5 6 Strongly Agree*

## Evaluation Form: *(Continued from previous page)*

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 answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

### Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

| | |
|---|---|
| 1. Describe the treatment challenges in patients with chronic HCV undergoing standard treatment. | 1 2 3 4 5 |
| 2. Enumerate the novel therapies currently in research to improve HCV treatment outcome. | 1 2 3 4 5 |
| 3. Predict how new agents and combinations of agents may be used in the future to improve efficacy of HCV treatment. | 1 2 3 4 5 |
| 4. Review how new agents and combinations of agents may be used in the future to improve patient adherence of HCV treatment. | 1 2 3 4 5 |

### Overall Effectiveness of the Activity

The content presented:

| | |
|---|---|
| Was timely and will influence how I practice | 1 2 3 4 5 |
| Enhanced my current knowledge base | 1 2 3 4 5 |
| Addressed my most pressing questions | 1 2 3 4 5 |
| Provided new ideas or information I expect to use | 1 2 3 4 5 |
| Addressed competencies identified by my specialty | 1 2 3 4 5 |
| Avoided commercial bias or influence | 1 2 3 4 5 |

### Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

_____

Please list any topics you would like to see addressed in future educational activities. _____

_____

Additional comments about this activity. _____

### Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |

### Request for Credit

Name _____ Degree _____

Organization _____ Specialty _____

Address _____

City, State, Zip _____

Telephone _____ Fax _____ E-mail _____

Signature _____ Date _____

**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.

PIM Postgraduate Institute for Medicine

Project ID: 5542