

Sofosbuvir Plus Ribavirin as a Treatment Alternative for Chronic HCV Genotype 2 or 3 Patients Unable to Benefit From Standard Therapy

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The combination of peginterferon and ribavirin is considered a standard of therapy for patients chronically infected with either genotype 2 or 3 hepatitis C virus (HCV). This regimen is associated with high rates of sustained virologic response (SVR) in both untreated and previously treated patients (70%-85% and 55%-60% response rates in each group, respectively).¹⁻⁴ However, there is currently a major gap in the field of hepatitis treatment of patients with HCV genotype 2 or 3 who are either unable to be treated with peginterferon or who previously failed to have a response to peginterferon. The number of patients affected by this is not insignificant; one report estimated that this patient group comprises the majority of HCV-infected patients.⁴

Thus, treatment alternatives are needed for chronically HCV-infected patients who are either unable to be treated with peginterferon or who previously failed to have a response to peginterferon. One potential treatment is the oral nucleotide analogue sofosbuvir. In vitro studies show that sofosbuvir is active across all HCV genotypes.⁵ A phase 2 trial in patients with chronic HCV infection (either genotype 2 or 3) found that treatment with sofosbuvir plus ribavirin resulted in a SVR in 100% (10 of 10) of previously untreated patients and 68% (17 of 25) of previously treated patients.^{6,7} Based on this, 2 phase 3 trials were designed to evaluate sofosbuvir plus ribavirin specifically in genotype 2 or 3 HCV-infected patients in whom either peginterferon therapy was not an option or who had previously failed to respond to peginterferon.⁸

Study Description

Two multicenter, randomized, clinical trials were conducted in patients with either genotype 2 or 3 chronic HCV infection.⁸ In both studies, sofosbuvir and ribavirin were administered orally. Sofosbuvir was given at a dose of 400 mg once daily, while ribavirin was administered

twice daily at doses that were determined by body weight. Patients with a body weight less than 75 kg were given 1000 mg ribavirin daily, while patients with a body weight of 75 kg or greater were given 1200 mg ribavirin daily.

In both studies, patients were screened at baseline by measurement of both serum HCV RNA levels as well as interleukin 28B (*IL-28B*) genotyping, in addition to standard laboratory assessments and clinical examinations. HCV RNA was detected via a real-time polymerase chain reaction (PCR) method, which was sensitive down to 25 IU/mL. *IL-28B* genotype was determined by PCR amplification followed by sequencing to assess the status of the rs12979860 single nucleotide polymorphism. Over the course of the study, patients were assessed using HCV RNA levels, standard vital signs, and symptom-driven physical examination. During the study, if a patient showed evidence of virologic failure, he or she underwent resistance testing that consisted of analysis of nucleotide mutations within the HCV *N588* gene. Mutation testing was performed in baseline samples as well as samples from the time of virologic failure.

The first trial, the POSITRON study, was a blinded study that compared the safety and efficacy of sofosbuvir plus ribavirin given over 12 weeks with matched placebo. This study enrolled patients for whom interferon treatment was not an option, due to either prior discontinuation resulting from unacceptable adverse events, a comorbidity that prevented treatment with interferon, or another reason that had caused the patient to decide against interferon treatment. Patients were not excluded due to prior interferon treatment failure.

In the POSITRON study, patients were enrolled at 63 sites throughout the United States, Canada, Australia, and New Zealand over the course of a 3-month period (March to May 2012). A total of 280 patients were randomized in a 3:1 fashion to receive sofosbuvir plus ribavirin or placebo; 278 patients actually began treat-

ment. Compensated cirrhosis was allowed at baseline in approximately 20% of patients enrolled in the study; the presence or absence of cirrhosis at baseline was used as a stratification factor in randomization.

The baseline characteristics were well balanced between the treatment groups, with a mean patient age of 52 years for each arm. In the sofosbuvir-plus-ribavirin group, 53% of patients had genotype 2 HCV, and 47% had genotype 3 HCV. In the placebo group, 48% of patients had genotype 2 HCV, and 52% had genotype 3 HCV. The mean HCV RNA level was $6.3 \pm 0.77 \log_{10}$ IU/mL in the treatment arm and $6.3 \pm 0.76 \log_{10}$ IU/mL in the placebo arm. High HCV RNA levels ($\geq 800,000$ IU/mL) were detected in 72% and 77% of patients in the sofosbuvir-plus-ribavirin and placebo arms, respectively. Cirrhosis was present at baseline in 15% of patients in the sofosbuvir-plus-ribavirin arm and 18% of patients in the placebo arm. Interferon was not available for these patients primarily due to the patient's own decision (42%-49%), a contraindication (most frequently a clinically significant psychiatric disorder or an autoimmune disorder; 43%-46%), or intolerable adverse events (8%-11%).

In this study, 78% of patients in the sofosbuvir-plus-ribavirin treatment group achieved a SVR at 12 weeks posttreatment. Comparatively, none of the patients in the placebo group had a SVR in the same time period ($P < .001$). Importantly, patients with genotype 3 HCV infection had significantly reduced rates of SVR compared with patients with genotype 2 HCV infection (61% vs 93%). The presence of cirrhosis at baseline also greatly impacted the response rates; 81% of patients without cirrhosis achieved a SVR compared with only 61% of patients with cirrhosis. Among the cirrhotic patients who responded, the HCV genotype appeared to have an important impact (94% of patients with HCV genotype 2 and cirrhosis compared with only 21% of patients with HCV genotype 3 and cirrhosis).

The second trial was the FUSION study, a blinded, active-controlled trial that compared 2 different treatment durations (12 weeks vs 16 weeks) of sofosbuvir plus ribavirin. This study enrolled patients who had previously failed to achieve a response to or had relapsed with an interferon-containing regimen.

The FUSION study enrolled patients from 67 sites throughout the United States, Canada, and New Zealand between May and July 2012. In a total of 202 patients, randomization was performed in a 1:1 fashion to treatment with either 12 or 16 weeks of sofosbuvir plus ribavirin; 201 patients actually began treatment. Patients in the 12-week group were treated with an additional 4 weeks of matched placebo. Approximately 30% of enrolled patients were allowed to have compensated cirrhosis at baseline, which served as a stratification factor at randomization.

Infection with either genotype 2 or 3 HCV also was used to stratify patients at randomization.

Baseline characteristics were well balanced between the 12-week and 16-week treatment arms; the mean patient age was 54 years in each arm. Most patients had genotype 3 HCV (64% in the 16-week group and 62% in the 12-week group), while fewer had genotype 2 HCV (33% in the 16-week group and 35% in the 12-week group). Three patients in each treatment group were found to have genotype 1 HCV infection using deep sequencing after randomization; these patients were excluded from the efficacy analysis but not the safety analysis. The mean HCV RNA levels at baseline were $6.5 \pm 0.63 \log_{10}$ IU/mL and $6.5 \pm 0.67 \log_{10}$ IU/mL in the 16-week and 12-week groups, respectively. A similar proportion of patients (79% in the 16-week and 78% in the 12-week groups) had HCV RNA levels at baseline that were at or greater than 800,000 IU/mL. Cirrhosis was present at baseline in 33% (16-week) and 35% (12-week) of patients. Approximately one-quarter of patients in this study were classified as having a nonresponse to prior therapy; the remaining patients had relapsed.

The patients treated with sofosbuvir plus ribavirin, regardless of treatment duration, achieved superior rates of SVR compared with the historical control population (50% and 73% in the 12-week and 16-week groups, respectively, compared with 25% in the control group; $P < .001$). The rates of SVR between the 2 treatment durations were found to be significantly higher with the longer 16-week treatment course (difference of 23%; $P < .001$). As was found in the POSITRON study, patients with genotype 3 HCV infection had lower response rates compared with genotype 2 HCV infection, an effect that was observed with both the 12-week (30% vs 86%) and 16-week (62% vs 94%) treatment groups. Cirrhosis also was found to be negatively associated with response in these patients, especially among patients with genotype 3 HCV infection. In the 12-week group, the rate of SVR was 61% among patients without cirrhosis at baseline (96% with genotype 2 HCV infection and 37% with genotype 3 HCV infection). This rate dropped to 31% among patients with cirrhosis at baseline (60% and 19% of patients with genotype 2 HCV and genotype 3 HCV infection, respectively). In the 16-week treatment group, 76% of the noncirrhotic patients (100% with genotype 2 HCV and 63% with genotype 3 HCV infection) and 66% of the cirrhotic patients (78% with genotype 2 HCV and 61% with genotype 3 HCV infection) achieved a SVR.

Overall, in both the POSITRON and FUSION studies, there were no cases of virologic breakthrough with sofosbuvir-plus-ribavirin treatment. A total of 115 patients (42 in the POSITRON study and 73 in the FUSION

study) had a relapse posttreatment; no resistance-associated variants were identified in any of these cases.

In the safety analysis of the POSITRON study, fatigue and insomnia occurred at a higher rate in the sofosbuvir-plus-ribavirin-treated patients compared with the placebo-treated patients (fatigue, 44% vs 24%; insomnia, 19% vs 4%). Anemia also occurred more frequently in patients receiving sofosbuvir plus ribavirin. In the FUSION study, the incidence of adverse events did not differ significantly between the 12-week and 16-week groups. In both studies, the overall rate of sofosbuvir-plus-ribavirin treatment discontinuation was low (1%-2%). For both studies, the overall toxicity profile was not significantly affected by the presence or absence of cirrhosis at baseline.

Overall, both the POSITRON and FUSION studies showed that treatment with sofosbuvir plus ribavirin resulted in a profound decrease in circulating levels of HCV RNA, among both genotype 2 and 3 HCV-infected patients. This decline was rapid, with 81% to 91% of sofosbuvir-plus-ribavirin-treated patients having HCV RNA levels that were less than the lower limit of assay quantitation by Treatment Week 2. This increased to 97% to 99% of sofosbuvir-plus-ribavirin-treated patients by Treatment Week 4. By the end of the treatment period, no evaluable patient who had been treated with sofosbuvir plus ribavirin had a quantifiable HCV RNA level.

Clinical Relevance

Together, these 2 studies suggest that sofosbuvir plus ribavirin is an effective treatment alternative for patients with chronic HCV infection. Specifically, this regimen was active in patients who are not candidates for, fail to respond to, or (for other reasons) decline treatment with peginterferon plus ribavirin. Although patients infected with genotype 2 HCV may require only 12 weeks of sofosbuvir-plus-ribavirin treatment, a longer treatment duration (16 weeks) may be required in patients infected

with genotype 3 HCV or in those patients with cirrhosis prior to therapy. The reason for the lower rates of SVR among patients with genotype 3 HCV infection is not known, especially in light of the fact that these patients exhibit rapid and profound virologic declines during treatment that are similar to those seen in patients with genotype 2 HCV infection. It is possible that patients with genotype 3 HCV infection have slower rates of virologic clearance, thus making these patients more susceptible to relapse resulting from residual viral reservoirs. Future studies with longer treatment durations—up to 24 weeks—may help resolve the difference observed among patients with genotype 3 HCV infection. Alternatively, patients with genotype 3 HCV infection may benefit from the addition of agents to allow more potent antiviral suppression and greater viral clearance. One such regimen was recently reported to be successful in patients infected with genotype 1, 4, 5, or 6 HCV⁹ and can be tested in the future in patients infected with genotype 3 HCV.

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Commentary

Sofosbuvir for Treatment of Hepatitis C Virus Genotype 2 or 3 Infection in Patients Without Treatment Options

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Chronic hepatitis C virus (HCV) infection is a major cause of morbidity and mortality worldwide. In the setting of cirrhosis, complications such as ascites, hepatic encephalopathy, or esophagogastric variceal bleeding may develop in afflicted patients. Furthermore, hepatocellular carcinoma is not uncommon in the setting of cirrhosis. Chronic HCV is the leading indication for liver transplantation in the United States.

Chronic HCV is characterized by different genotypes (GTs). GT 1 is the most common in the United States. The direct-acting antiviral agents telaprevir (Incivek, Vertex) and boceprevir (Victrelis, Merck) are approved for use only for GT 1. GT 2 and 3 are less common in the United States, but a significant number of patients are affected. The standard therapy for HCV GT 2 or 3 is a course of pegylated interferon (PEG) and ribavirin (RBV) for 24 weeks.¹⁻³ Sustained virologic response (SVR) rates of 70% to 85% are to be expected. Nevertheless, 15% to 30% of treated patients either experience virologic relapse or nonresponse and, thus, fail therapy. PEG and RBV therapy is complicated by numerous adverse effects, including flulike symptoms, psychiatric symptoms, cytopenias, thyroid issues, hair loss, and skin rash among others.^{2,4} Many patients are fearful of these adverse effects and elect not to pursue therapy. Furthermore, many patients have contraindications to therapy with PEG and are ineligible for therapy. These include patients with psychiatric diseases such as bipolar disorder or depression, autoimmune disease such as rheumatoid arthritis or psoriasis, and cytopenias. Patients with HCV GT 2 or 3 who have failed therapy or who are ineligible or refuse to

take PEG have no therapeutic options and represent a significant unmet medical need.

Well-tolerated and more efficacious regimens are sought. An ideal regimen would be effective in patients who have failed standard therapy. In addition, the regimen would not include PEG, the medication that is responsible for most of the adverse effects with the standard regimen. An oral regimen that is administered over a relatively short time period with a favorable daily dosing schedule and without drug-drug interactions would be optimal.

Sofosbuvir (SOF) is an oral nucleotide analogue inhibitor of the HCV-specific NS5B polymerase enzyme. In vitro studies have shown that SOF has pangenotypic activity.^{3,5} In phase 2 trials, excellent tolerability and efficacy were observed in a small number of patients with HCV GT 2 or 3 who were either treatment-naïve or treatment-experienced.^{4,6,7}

POSITRON was a multicenter, randomized, blinded, placebo-controlled trial assessing SOF 400 mg once daily plus RBV (1000-1200 mg in divided doses based on weight) for 12 weeks in patients with HCV GT 2 or 3 who previously did not tolerate interferon, who had contraindications for interferon, or who had refused interferon.

FUSION was a multicenter, randomized trial assessing SOF and RBV at the aforementioned dosages for either 12 or 16 weeks in patients with HCV GT 2 or 3 who had previously not achieved SVR after a previous course of PEG plus RBV.

Patients with cirrhosis were included in both trials. The primary endpoint was SVR12 identified by undetectable HCV RNA 12 weeks after discontinuation of antiviral therapy. The FUSION trial compared SVR rates with an expected historical control SVR of 25%.

These studies' findings represent a substantial advance in the treatment of chronic HCV infection. These are the first published phase 3 trials examining an interferon-free regimen (ie, SOF and RBV) in patients with HCV GT 2

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or 3. FUSION is the first study that assessed a therapeutic option for patients with HCV GT 2 or 3 that have previously failed therapy. POSITRON is the first study that has been published investigating patients with GT 2 or 3 in whom interferon was not an option. Although patients with GT 2 or 3 HCV infection are not as common as GT 1 in the United States, physicians who care for patients with HCV have patients in their practice who have failed standard therapy, who have not tolerated therapy, who have contraindications to therapy, or who refuse therapy that would be appropriate.

These studies present several interesting findings. First, an oral regimen (interferon-free) is shown to be effective in patients with GT 2 or 3. Interestingly, RBV appears to be well tolerated when given in a setting without interferon. Fatigue, insomnia, and anemia were reported in a relatively small number of patients on active treatment compared with patients receiving placebo in the POSITRON trial. The adverse events were mild and tolerable.

Patients with GT 3 did less well than those with GT 2. This has previously been reported with PEG-plus-RBV therapy as well.^{5,8} In patients with GT 2, patients do extremely well with a 12-week course of SOF plus RBV. In patients with GT 3, SVR is lower. Although SVR12 is reasonable in a group of patients without other therapeutic options, the efficacy in this population is not optimal. In particular, cirrhotic patients with GT 3 do not do well with SOF plus RBV.

For patients with GT 3 who did not achieve SVR after a previous course of PEG plus RBV, a 16-week course is favorable compared with a 12-week course. GT 2 patients do better than GT 3 patients. A 12-week course for noncirrhotic patients who have previously failed therapy may suffice. However, for cirrhotic patients with GT 2, a 16-week course appears to be of more benefit.

The optimal length of therapy with SOF and RBV for patients with cirrhosis and GT 2 or 3 who previously failed standard therapy is unclear. Sixteen-week regimens provided increased efficacy compared with 12-week regimens. Longer regimens must be investigated in clinical trials. Furthermore, additional viral suppression with direct-acting antiviral agents with different mechanisms of action or with immunomodulating agents may be helpful to augment SVR. Future studies are awaited.

Take-Home Points

The regimen of SOF plus RBV satisfies many of the characteristics of an optimal treatment regimen for patients

with GT 2 or 3 HCV infection. The regimen is oral, the administration of medications is favorable (SOF 400 mg once daily and RBV 1000-1200 mg daily in divided doses), and the treatment course is relatively short (12-16 weeks). Furthermore, the regimen is well tolerated, and there are no drug-drug interactions. No resistance-associated variants were identified. Efficacy is excellent, especially in patients with GT 2.

It appears that, in the near future, many patients with GT 2 or 3 who previously had no options will be treated; included are patients who failed or could not tolerate therapy with PEG plus RBV, those with contraindications to PEG plus RBV, or those who refuse to take PEG plus RBV. This regimen will change clinical practice and have a substantial impact on treatment of patients with GT 2 or 3 HCV infection.

For patients with GT 2 in whom interferon is not an option, a 12-week course of SOF-plus-RBV therapy offers excellent tolerability and efficacy. For patients with GT 3 in whom interferon is not an option, a 12-week course offers excellent tolerability and reasonable efficacy. For noncirrhotic patients with GT 2 who previously failed PEG plus RBV, a 12-week course offers excellent efficacy. For cirrhotic patients with GT 2 or 3 who failed PEG plus RBV in the past, a 16-week course offers improved efficacy. It is possible that a longer course will further improve response rates.

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