Simeprevir and sofosbuvir for treatment of hepatitis C infection

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A pproximately 150 million people worldwide have chronic hepatitis C virus (HCV) infection, with an additional 3–4 million people becoming newly infected annually. In the United States, an estimated 2.7–3.9 million persons are living with HCV infection, and an additional 17,000 individuals are newly infected each year. HCV-related liver disease accounts for more than 350,000 deaths each year and is the leading indication for liver transplantation. For the first time, the number of annual deaths from HCV infection has exceeded those associated with human immunodeficiency virus (HIV) infection. Past therapies for hepatitis C are not 100% effective in producing a sustained virological response (SVR) or an undetectable level of HCV RNA in the blood, considered a clinical cure. Newer therapies are inching closer toward full eradication of HCV; however, achievement of this endpoint currently requires the use of complex regimens with multiple medications for extended periods of time.

First identified in 1989, HCV is a small, enveloped, single-stranded RNA virus belonging to the family Flaviviridae and the genus Hepacivirus. HCV RNA encodes a single, large polypeptide that is posttranslationally cleaved into several structural and nonstructural active peptides. The structural elements include the nucleocapsid core and two envelope glycoproteins that facilitate virus entry into host cells. Nonstructural proteins include p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. Although

Purpose. The pharmacology, pharmacokinetics, efficacy, safety, costs, and place in therapy of simeprevir and sofosbuvir in the management of hepatitis C virus (HCV) infection are reviewed.

Summary. Sofosbuvir and simeprevir are classified as direct-acting agents because they target specific proteins essential to the replication of HCV. Phase III trials demonstrated that simeprevir in combination with peginterferon alfa and ribavirin was superior to placebo combined with peginterferon alfa and ribavirin in achieving a sustained virological response in both treatment-naive patients and patients who relapsed after treatment with peginterferon alfa-2a or alfa-2b and ribavirin. Q80K polymorphism substantially decreases the efficacy of simeprevir. Clinical trials revealed that sofosbuvir in combination with ribavirin was superior to peginterferon plus ribavirin against HCV genotype 2 infection and as effective as peginterferon plus ribavirin against HCV genotype 3 infection. These findings were significant because they demonstrated the effectiveness of an anti-HCV regimen that did not include peginterferon alfa. Sofosbuvir has much better adverse-effect and drug interaction profiles than previous hepatitis C antiviral agents. Both simeprevir and sofosbuvir are approved for the treatment of chronic hepatitis C in combination with other antiviral medications. Simeprevir has been approved specifically for patients infected with HCV genotype 1 with compensated liver disease (including cirrhosis) in combination with peginterferon alfa-2a or alfa-2b and ribavirin. Sofosbuvir has shown efficacy in HCV genotypes 1-4.

Conclusion. Simeprevir and sofosbuvir have advantages in response rates and convenient dosage forms and frequency compared with other HCV treatments; however, they are more expensive than previous HCV therapies.

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not essential for viral replication, the p7 protein associates itself with the host endoplasmic reticulum and facilitates formation of infectious virions. NS2 and NS3 are viral proteases.\textsuperscript{3} NS3 has NTPase and helicase activity and forms a complex with NS4A (a cofactor of the protease). NS4B is located in the endoplasmic reticulum and helps recruit other viral proteins. NS5A binds to the endoplasmic reticulum–anchored virus-associated particles, a critical role in viral replication and interferon response. NS5B facilitates viral replication by acting as an RNA polymerase.

The most common means by which HCV is transmitted is the sharing of contaminated needles, syringes, or other paraphernalia for injection drug use. After the initial infection, virus replication begins quickly, yielding detectable HCV RNA levels in the blood within one to two weeks and peak HCV viral loads in six to eight weeks.\textsuperscript{4} At this time, alanine transaminase levels begin to rise, and patients may become acutely symptomatic. Anti-HCV antibodies also develop in immuno-competent individuals around this time, resulting in almost undetectable levels of circulating HCV RNA one year after infection.\textsuperscript{4} However, 60–85% of patients do not clear the HCV from their bodies and decades later can suffer chronic infection with consequential hepatocellular destruction, cirrhosis, and hepatocellular carcinoma.\textsuperscript{4}

To date, 6 genotypes and over 50 subtypes of HCV have been identified.\textsuperscript{4} In the United States, genotype 1a is most commonly associated with infection; however, genotype 1b is more frequently detected worldwide. Genotypes 1a and 1b account for approximately 75% of HCV infections in the United States, whereas genotypes 2a and 2b and genotype 3a are recovered from 13–15% and 6–7% of cases of chronic hepatitis, respectively.\textsuperscript{4} It is important to note that the infecting genotype is associated with treatment response. Historically, individuals infected with genotype 2 or 3 were twice as likely to respond to treatment as those infected with genotype 1.\textsuperscript{4} Furthermore, patients infected with genotype 1b had a better chance of achieving an SVR than did those with HCV genotype 1a. This may be due to the fact that the NS3 Q80K polymorphism is present in some patients with HCV genotype 1a. This polymorphism has resulted in reduced efficacy of some medications. Genotypes 4–6 are rarely encountered in the United States and are mostly found in Africa and Asia.\textsuperscript{4}

Current treatment strategies for hepatitis C rely heavily on the selection of agents that are active against the specific HCV genotype isolated. Historically, the combination of peginterferon alfa-2a or alfa-2b plus ribavirin was the standard of therapy for HCV genotypes 2 and 3. However, response rates to this regimen in patients infected with HCV genotype 1 are typically less than 40%.\textsuperscript{5} In 2011, the Food and Drug Administration (FDA) approved the labeling for NS3/4A protease inhibitors telaprevir and boceprevir for use in combination with peginterferon alfa-2a or alfa-2b and ribavirin to treat HCV genotype 1 infections.\textsuperscript{5} Although these agents markedly improved response rates among individuals with HCV genotype 1, response rates were still less than optimal, and the regimens still required the use of peginterferon alfa-2a or alfa-2b and ribavirin. Patients receiving these three drug regimens had to contend with a constellation of adverse effects, including aggravation of neuropsychiatric conditions, autoimmune diseases, infections, and anemia. Furthermore, regimens were confusing, drug–drug interactions were common, and follow-up was complicated.

The search for more effective and better-tolerated treatments for HCV infection has accelerated over the past decade. Antivirals targeting a variety of viral proteins and steps in the HCV life cycle are under investigation. On November 22, 2013, simeprevir (Olysio, Janssen Pharmaceuticals) was approved by FDA for the treatment of chronic HCV infection as part of an antiviral treatment regimen in combination with peginterferon alfa-2a or alfa-2b and ribavirin in HCV genotype 1–infected adults with compensated liver disease, including cirrhosis.\textsuperscript{6} On December 6, 2013, sofosbuvir (Sovaldi, Gilead Sciences) was approved as a component of combination antiviral treatment in patients with HCV genotype 1, 2, 3, or 4 infection, including patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those coinfected with HIV-1.\textsuperscript{7} The advent of these new antivirals quickly changed the face of hepatitis C treatment. The remainder of this article reviews the pharmacology, pharmacokinetics, efficacy, and safety of simeprevir and sofosbuvir and discusses the place in therapy of these agents in the management of HCV infection.

**Pharmacology**

Sofosbuvir and simeprevir are classified as direct-acting agents because they target specific proteins essential to the replication of HCV.

**Simeprevir.** Simeprevir is a NS3/4A protease inhibitor, similar to boceprevir and telaprevir. These agents interfere with the cleavage of the HCV polyprotein at the NS3/4A, NS4A/4B, NS4B/5A, and NS5A/5B junctions during viral replication.\textsuperscript{5} This action results in a lack of production of the active structural and nonstructural proteins and cessation of virus production.\textsuperscript{5} First-generation NS3/4A protease inhibitors exert activity against HCV genotype 1; however, second-generation candidates (e.g., simeprevir, danoprevir) have demonstrated activity against other genotypes as well.\textsuperscript{5} Unfortunately,
NS3/4A protease inhibitors have a low genetic barrier to resistance. Substitutions near the NS3 protease catalytic site alter the affinity to the enzyme for the protease inhibitors, resulting in reduced activity; however, they do not affect the overall fitness of the virus. Mutations imparting resistance to NS3/4A protease inhibitors have been found in nature and occur rapidly after monotherapy with these agents. Mutations, such as the NS3 Q80K polymorphism, have been shown to decrease simeprevir’s efficacy in genotype 1a patients. Thus, screening for the NS3 Q80K polymorphism before initiating treatment with these agents is strongly recommended. If patients test positive for the polymorphism, alternative therapy should be considered.

Sofosbuvir. Sofosbuvir is the first drug in a class of anti-HCV agents called the NS5B nucleoside–nucleotide analog inhibitors. Medications in this class mimic the pyrimidine nucleotide biosynthesis pathway. GS-461203 eventually undergoes dephosphorylation to the active terminal metabolite GS-331007. After the administration of a single dose, approximately 80% of sofosbuvir (3.5% parent compound and 78% GS-331007) is recovered in the urine. The terminal half-lives of sofosbuvir and GS-331007 are 0.4 and 27 hours, respectively.

Clinical efficacy

Simeprevir. The approval of simeprevir was largely supported by the results of two Phase IIb trials (PILLAR and ASPIRE) and three Phase III clinical trials (QUEST 1, QUEST 2, and PROMISE).

Phase II trials. The PILLAR study was a Phase IIb, randomized, double-blind, five-group, placebo-controlled trial consisting of treatment-naïve patients with chronic HCV genotype 1 infections. The primary endpoint was an SVR at week 72. The study was intended to provide insight into the safety and efficacy of simeprevir (75 or 150 mg daily for 12 or 24 weeks) in combination with peginterferon alfa and ribavirin for 24 or 48 weeks. The results were used only for ancillary safety data in assessing simeprevir for the FDA antiviral drugs advisory committee meeting in 2013. No published results were reported for this study.
The ASPIRE study was a Phase IIb, randomized, double-blind, seven-group, placebo-controlled trial investigating the safety and efficacy of various simeprevir regimens. The trial included patients who had chronic HCV infection and had previously not responded to treatment, partially responded to treatment, or relapsed after receiving at least one course of peginterferon alfa and ribavirin therapy. There was no mention of excluding patients infected with a Q80K polymorphism. A total of 462 patients were randomized in a 1:1:1:1:1:1:1 fashion to receive a combination of (1) placebo plus peginterferon alfa-2a and ribavirin for 48 weeks or (2) simeprevir 100 or 150 mg daily for 12, 24, or 48 weeks combined with peginterferon alfa-2a and ribavirin for 48 weeks. The primary endpoint of this trial was an SVR (HCV RNA concentration of <25 IU/mL or an undetectable HCV RNA concentration) at 24 weeks after the end of treatment (SVR24). The patient population, regardless of study group, was divided into categories based on their response to previous therapy: relapsers, partial responders, and null responders. Overall, SVR24 rates were higher in simeprevir-treated patients regardless of HCV genotype 1 subtype, METAVIR fibrosis score (an algorithm for the grading of activity in chronic hepatitis), and IL28B genotype (Table 1). The limitations noted in this study were a small sample size (65–68 patients per group) and an SVR24 rate that was two times greater than predicted in the null responder group receiving placebo. The results of this trial supported the use of simeprevir in partial or null responders to peginterferon alfa and ribavirin therapy.

**Phase III trials.** The QUEST 1 and QUEST 2 trials assessed the efficacy of simeprevir in treatment-naïve patients with chronic HCV genotype 1 infection. In both of these randomized, double-blind, placebo-controlled, two-group, multicenter trials, the primary outcome was an SVR (HCV RNA concentration of <25 IU/mL or an undetectable HCV RNA concentration) at 12 weeks after the end of treatment (SVR12). Subgroup analyses were conducted using the data from patients in the simeprevir group with genotype 1a and with the Q80K polymorphism.

In the QUEST 1 trial, 394 patients were randomized to receive simeprevir 150 mg orally once daily in combination with peginterferon alfa-2a (180 μg weekly) and ribavirin (1000 mg daily for patients weighing less than 75 kg and 1200 mg daily for patients weighing 75 kg or more) for 12 weeks followed by peginterferon alfa-2a and ribavirin alone for 12 or 36 weeks, based on the patient’s response, or to receive placebo in combination with peginterferon alfa-2a and ribavirin for 12 weeks followed by peginterferon alfa-2a and ribavirin alone for an additional 36 weeks. SVR12 was observed in 210 (80%) of 264 patients treated with simeprevir, peginterferon alfa-2a, and ribavirin compared with 65 (50%) of 130 patients who received placebo, peginterferon alfa-2a, and ribavirin (adjusted difference, 29.3%; 95% confidence interval [CI], 20.1–38.6%; p < 0.0001). In the QUEST 2 trial, 391 patients were randomized to receive simeprevir 150 mg daily plus peginterferon alfa-2a (180 μg or peginterferon alfa-2b (50, 80, 100, 120, or 150 μg) administered at 1–5 μg/kg of body weight once weekly and ribavirin (1000–1200 mg or 800–1400 mg daily, depending on formulation) for 12 weeks followed by peginterferon alfa and ribavirin alone for 12 or 36 weeks in accordance with the on-treatment protocol-defined response guided therapy criteria (HCV RNA concentration of <25 IU/mL at week 4 as well as an undetectable HCV RNA concentration at week 12 or control). The control in the QUEST 2 trial was identical to that used in the QUEST 1 trial—a simeprevir-like placebo for 12 weeks in combination with peginterferon alfa-2a or alfa-2b and ribavirin for 48 weeks. SVR12 was observed in 209 (81%) of 257 patients in the simeprevir group and 67 (50%) of 134 patients who received placebo (adjusted difference, 32.2%; 95% CI, 23.3–41.2%; p < 0.0001).

The results of the QUEST 1 and QUEST 2 trials were pooled for the manufacturer’s new drug application due to their nearly identical study designs. The pooled primary endpoint results are summarized in Table 2. In a subgroup analysis, patients in the simeprevir group with genotype 1a (without Q80K baseline polymorphism) and genotype 1b had similar SVR12 rates (84% and 85%, respectively). When combined, only 43% of the control group achieved SVR12. No significant difference in response was seen between the treatment (58%) and control (55%) groups in patients with the Q80K polymorphism. The presence of the Q80K polymorphism is associated with an approximate 10-fold reduction in susceptibility to simeprevir. Since the Q80K polymorphism in HCV genotype 1a is common in the U.S. population, the investigators suggested that all patients with genotype 1a should be screened for this polymorphism.

The PROMISE trial was a Phase III, randomized, double-blind, placebo-controlled study in patients with chronic HCV genotype 1 infection who relapsed after receiving at least 24 weeks of peginterferon alfa and ribavirin therapy and were within one year of their last medication dose. Of the 393 patients, 260 were randomized to receive simeprevir 150 mg daily in combination with peginterferon alfa-2a (180 μg weekly) and ribavirin (1000 or 1200 mg daily, depending on body weight) for 12 weeks, followed by peginterferon alfa-2a and ribavirin alone for 12 or 36 weeks, based on their response to therapy. The remaining 133 received...
simeprevir for 12 weeks in combination with peginterferon alfa-2a and ribavirin for 48 weeks. Similar to the QUEST 1 and QUEST 2 trials, the primary endpoint was SVR12 (Table 2). In a subgroup analysis, 47% and 78% of patients with and without the Q80K polymorphism in the simeprevir-treated group achieved SVR12, respectively. The results of the PROMISE trial emphasize the importance of testing for the Q80K polymorphism in all patients with HCV genotype 1a.

In summary, the results of Phase III trials demonstrated that simeprevir in combination with peginterferon alfa and ribavirin was superior to placebo combined with peginterferon alfa and ribavirin in achieving an SVR in both treatment-naive patients and patients who relapsed after treatment with peginterferon alfa-2a or alfa-2b and ribavirin. It is important to note that the Q80K baseline polymorphism substantially decreases the efficacy of simeprevir. The Infectious Diseases Society of America now recommends that all patients infected with HCV genotype 1 undergo screening for this polymorphism before initiating simeprevir therapy. It is also important to note that patients with moderate or severe hepatic impairment, as well as those of East Asian descent, had sizable increases in simeprevir exposure and thus are at risk for adverse medication-related effects. Therefore, the risks and benefits of using simeprevir in these populations must be considered, and dosage reductions may be warranted.

**Sofosbuvir.** Numerous trials have been published documenting the safety and clinical efficacy of sofosbuvir. The primary efficacy endpoint in these trials was SVR (HCV RNA concentration below the lower limit of quantification) at 12, 16, or 24 weeks.

**Phase II trials.** The ELECTRON trial was a Phase Ia, open-label trial designed to evaluate the safety and efficacy of sofosbuvir 400 mg daily plus weight-based doses of ribavirin twice daily in various peginterferon-sparring and peginterferon-free regimens in patients infected with HCV genotype 1, 2, or 3. In the first part of the trial, subjects with HCV genotype 2 or 3 were randomly assigned to one of four treatment groups: (1) sofosbuvir 400 mg daily plus ribavirin for 12 weeks \( (n = 10) \), (2) sofosbuvir 400 mg daily plus ribavirin for 12 weeks, followed by peginterferon alfa-2a 180 \( \mu g \) once weekly for 4 weeks \( (n = 9) \), (3) sofosbuvir 400 mg daily plus ribavirin for 12 weeks, followed by peginterferon alfa-2a 180 \( \mu g \) once weekly for 8 weeks \( (n = 9) \), and (4) sofosbuvir 400 mg daily plus ribavirin for 12 weeks, followed by peginterferon alfa-2a 180 \( \mu g \) once weekly for 12 weeks \( (n = 11) \). Ribavirin was dosed orally twice daily according to body weight (1000 mg in patients weighing less than 75 kg and 1200 mg in patients weighing 75 kg or more). In the second part of the trial, patients with HCV genotype 2 or 3 who were previously untreated were given sofosbuvir 400

### Table 1.
**Summary of ASPIRE Trial Results**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Intervention</th>
<th>% Patients Achieving Sustained Virological Response 24 Weeks After End of Treatment</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>Group 1 ( (n = 66) )</td>
<td>Simeprevir 100 mg daily + peginterferon alfa + ribavirin for 12 wk, followed by peginterferon alfa + ribavirin for 36 wk</td>
<td>73</td>
</tr>
<tr>
<td>Group 2 ( (n = 65) )</td>
<td>Simeprevir 100 mg daily + peginterferon alfa + ribavirin for 24 wk, followed by peginterferon alfa + ribavirin for 24 wk</td>
<td>66</td>
</tr>
<tr>
<td>Group 3 ( (n = 66) )</td>
<td>Simeprevir 100 mg + peginterferon alfa + ribavirin for 48 wk</td>
<td>61</td>
</tr>
<tr>
<td>Group 4 ( (n = 66) )</td>
<td>Simeprevir 150 mg + peginterferon alfa + ribavirin for 12 wk, followed by peginterferon alfa + ribavirin for 36 wk</td>
<td>67</td>
</tr>
<tr>
<td>Group 5 ( (n = 68) )</td>
<td>Simeprevir 150 mg + peginterferon alfa + ribavirin for 24 wk, followed by peginterferon alfa + ribavirin for 24 wk</td>
<td>72</td>
</tr>
<tr>
<td>Group 6 ( (n = 65) )</td>
<td>Simeprevir 150 mg + peginterferon alfa + ribavirin for 48 wk</td>
<td>80</td>
</tr>
<tr>
<td>Group 7 ( (n = 66) )</td>
<td>Peginterferon alfa + ribavirin for 48 wk</td>
<td>23</td>
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mg daily as monotherapy (n = 10) or sofosbuvir 400 mg daily plus peginterferon alfa-2a 180 µg once weekly and ribavirin (dosed by body weight) for 8 weeks (n = 10). Patients with HCV genotype 1 who (1) had not previously responded to at least 12 weeks of therapy with peginterferon alfa-2a and ribavirin (n = 10) or (2) had not previously received treatment for HCV infection (n = 25) were assigned to receive sofosbuvir plus ribavirin for 12 weeks. A total of 95 patients were enrolled in this trial. A majority of patients were white (n = 74) and male (n = 58). Patients' mean body mass index (BMI) was 26 kg/m², and their median HCV RNA concentration was 6.4 log₁₀ IU/mL. A total of 35 patients had IL28B genotype CC, 46 had IL28B genotype CT, and 14 had IL28B genotype TT. All 95 patients attained an SVR by treatment week 4. All patients with HCV genotype 2 or 3 achieved SVR₂₄ except for 4 of the 10 in the sofosbuvir monotherapy group. Of the 35 patients with HCV genotype 1, 22 achieved SVR₂₄. The study investigators concluded that sofosbuvir in combination with ribavirin was associated with achieving an SVR in all previously untreated patients with HCV genotype 2 or 3 and in the majority of previously untreated patients with HCV genotype 1.

The SPARE trial was a Phase II, single-center, two-part, randomized controlled trial of treatment-naive patients with chronic HCV genotype 1. In part 1 (proof of concept), patients received sofosbuvir 400 mg daily and weight-based ribavirin (400 mg in the morning and 400 mg in the evening for patients weighing more than 75 kg, or 600 mg twice daily for patients weighing more than 75 kg) for 24 weeks. In part 2, patients were randomized to receive sofosbuvir in combination with either weight-based ribavirin or low-dose ribavirin (600 mg daily) for 24 weeks. A total of 60 patients met the inclusion criteria; 10 patients in part 1 and 50 in part 2.

Table 2.
Summary of Simeprevir Phase III Trial Results

<table>
<thead>
<tr>
<th>Trial and Study Intervention</th>
<th>% Patients Achieving Sustained Virological Response</th>
<th>% Patients With Treatment Failure</th>
<th>% Patients With HCV Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUEST 1 (n = 394) and QUEST 2 (n = 391)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Simeprevir and peginterferon alfa-2a plus ribavirin for 12 wk, followed by peginterferon alfa plus ribavirin for 12 or 36 wk</td>
<td>80</td>
<td>58</td>
<td>85</td>
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<tr>
<td>Peginterferon alfa plus ribavirin for 48 wk</td>
<td>50</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>PROMISE (n = 393)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Simeprevir and peginterferon alfa plus ribavirin for 12 wk, followed by peginterferon alfa and ribavirin for 12 or 36 wk</td>
<td>79</td>
<td>47</td>
<td>86</td>
</tr>
<tr>
<td>Peginterferon alfa plus ribavirin for 48 wk</td>
<td>37</td>
<td>20</td>
<td>43</td>
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*aHCV = hepatitis C virus.
Simeprevir and sofosbuvir

The LONESTAR trial was a Phase II, randomized, open-label study that enrolled patients with chronic HCV genotype 1 infection who had not previously received treatment for HCV (cohort A) or had previously not responded to treatment with a protease inhibitor regimen (cohort B). Patients in cohort A were randomized to receive sofosbuvir 400 mg daily plus ledipasvir (a novel HCV NS5A inhibitor) 90 mg daily for 8 or 12 weeks or sofosbuvir plus ledipasvir with ribavirin (dosed according to body weight). Patients in cohort B were randomized to receive (1) sofosbuvir 400 mg daily plus ledipasvir 90 mg daily for 12 weeks or (2) sofosbuvir 400 mg daily plus ribavirin (based on body weight) and ledipasvir 90 mg daily for 12 weeks. A total of 100 patients were randomized. Compensated cirrhosis was not found in any patients in cohort A but was present in 55% of patients in cohort B. Baseline characteristics within each of the cohorts were similar among treatment groups. Most patients were nonblack, male, and approximately 50 years of age. Fifteen subjects had IL28B genotype CC, 61 had IL28B genotype CT, and 24 had IL28B genotype TT. All treatment groups achieved SVR12 rates of 95–100%. Relapse was seen in 2% of patients (1 in cohort A and 1 in cohort B). Although this study's sample was small, the combination of sofosbuvir and ledipasvir appeared promising among patients infected with HCV genotype 1 for whom interferon-based regimens were not feasible.

Phase III trials. The safety and efficacy of sofosbuvir have also been evaluated in four Phase III trials (Table 3). Three of these trials enrolled patients infected with HCV genotype 2 or 3, with an additional trial evaluating treatment efficacy and safety in patients with HCV genotype 1, 4, 5 or 6. The primary endpoint for all four trials was SVR12. The sofosbuvir-containing groups in all four trials used sofosbuvir 400 mg orally once daily in combination with a weight-based ribavirin dose (1000 mg daily in patients weighing less than 75 kg and 1200 mg daily in patients weighing 75 kg or more).

The FUSION study was a Phase III, randomized, multicenter, open-label, active-controlled trial involving treatment-naive patients with HCV genotype 2 or 3. Patients were randomly assigned to receive sofosbuvir plus ribavirin for 12 weeks (n = 256) or peginterferon alfa-2a 180 μg weekly plus ribavirin 800 mg daily for 24 weeks (n = 243). Of the 499 patients enrolled, 20% had compensated cirrhosis, 327 were male, and 435 were white. Patients' mean age was 48 years, mean BMI was 28 kg/m2, and mean HCV RNA concentration was 6.0 log10 IU/mL. A total of 214 patients had IL28B genotype CC, 219 had IL28B genotype CT, and 63 had IL28B genotype TT. The overall SVR12 was 67% in both treatment groups. In patients with HCV genotype 2, the SVR12 rate was 95% in those treated with sofosbuvir plus ribavirin versus 78% in the peginterferon plus ribavirin group. In patients with HCV genotype 3, the SVR12 rate was 56% in those treated with sofosbuvir plus ribavirin versus 63% in the peginterferon plus ribavirin group. When treated with sofosbuvir plus ribavirin, patients with HCV genotype 2 had a higher SVR12 rate and a lower relapse rate compared with patients with HCV genotype 3. The rates of adverse events were consistently lower in patients receiving sofosbuvir and ribavirin. This study demonstrated that treatment with sofosbuvir in combination with ribavirin for 12 weeks was superior to peginterferon plus ribavirin against HCV genotype 2 infection and as effective as peginterferon plus ribavirin against HCV genotype 3 infection. These findings were significant because they demonstrated the effectiveness of an anti-HCV regimen that did not include peginterferon alfa.

(25 patients in each group). Baseline characteristics were similar between groups. Eighty-three percent of study enrollees were black, 66% were men, 48% had a BMI exceeding 30 kg/m2, 81% had IL28B genotype CT or TT, 23% had advanced liver disease, and 62% had HCV RNA concentrations exceeding 800,000 IU/mL. SVR24 was achieved by 68% of patients receiving weight-based ribavirin compared with 48% of patients receiving low-dose ribavirin (95% CI, 81–92%; p = 0.2). The investigators concluded that the results did not show a significant association between treatment response and ribavirin dosing; therefore, the optimal dose and role of ribavirin in peginterferon-free HCV therapy remain to be established.

The ATOMIC trial was a Phase II, multicenter, randomized, open-label trial that enrolled treatment-naive patients with HCV genotype 1 or 4–6. Subjects were randomized into one of three cohorts: (1) sofosbuvir plus ribavirin and peginterferon alfa for 12 weeks (n = 52), (2) sofosbuvir plus ribavirin and peginterferon alfa for 24 weeks (n = 125), and (3) sofosbuvir plus ribavirin and peginterferon alfa for 12 weeks, followed by (a) an additional 12 weeks of sofosbuvir monotherapy or (b) an additional 12 weeks of sofosbuvir plus ribavirin (n = 155). Patients' mean age was 50 years, mean BMI was 28 kg/m2, and mean HCV RNA concentration was 6.4 log10 IU/mL. A total of 214 patients were male, 297 were of a nonblack race, 88 had IL28B genotype CC, 184 had IL28B genotype CT, and 60 had IL28B genotype TT. The results of this study demonstrated an SVR24 of 89% in cohort 1 (95% CI, 77–96%), 89% in cohort 2 (95% CI, 82–94%), and 87% in cohort 3 (95% CI, 81–92%). Relapse was seen in 7 patients (2 in cohort 1, 1 in cohort 2, and 4 in cohort 3). These findings suggest that sofosbuvir is well tolerated and that there is no additional benefit of extending sofosbuvir treatment beyond 12 weeks.
The POSITRON study was a Phase III, randomized, double-blind, multicenter trial that enrolled patients infected with HCV genotype 2 or 3 who were peginterferon alfa intolerant or ineligible or unwilling to take peginterferon alfa.\textsuperscript{20} Patients were randomized in a 3:1 ratio to receive either sofosbuvir plus ribavirin for 12 weeks (\textit{n} = 207) or placebo for 12 weeks (\textit{n} = 71). Of the 278 patients enrolled, 16\% had compensated cirrhosis. The majority of patients were white (\textit{n} = 254) and male (\textit{n} = 151). Patients’ mean age was 52 years, mean BMI was 28 kg/m\textsuperscript{2}, and mean HCV RNA concentration was 6.3 log\textsubscript{10} IU/mL. A total of 61 patients had HCV genotype 2, or 3 who had not responded to prior treatment with peginterferon alfa–based regimens.\textsuperscript{20} Patients were randomized in a 1:1 ratio to receive sofosbuvir plus ribavirin for 12 weeks (\textit{n} = 103) or 16 weeks (\textit{n} = 98). Of the 201 patients enrolled, 34\% had compensated cirrhosis. The majority of patients were white (\textit{n} = 174) and male (\textit{n} = 140). Patients’ mean age was 54 years, mean BMI was 28.5 kg/m\textsuperscript{2}, and mean HCV RNA concentration was 6.4 log\textsubscript{10} IU/mL. Ninety-five patients had HCV genotype 2, 126 patients had HCV genotype 3, and 120 had HCV genotype 4. Seventeen percent had HCV genotype 5, and 6 had HCV genotype 6. Seventeen percent of patients had compensated cirrhosis. Patients’ mean age was 52 years, mean BMI was 29 kg/m\textsuperscript{2}, and mean HCV RNA concentration was 6.4 log\textsubscript{10} IU/mL. Ninety-five patients had HCV genotype 2, 181 had HCV genotype 3, and 81 had HCV genotype 4. Overall, 90\% of subjects

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Trial and Intervention(s)} & \textbf{\% Patients With SVR12, by HCV Genotype} \\
\hline
\textbf{FISSION} & \\
Sofosbuvir plus ribavirin for 12 wk (\textit{n} = 256) & Genotype 2: 95 \\
Peginterferon alfa plus ribavirin for 24 wk (\textit{n} = 243) & Genotype 2: 78 \\
& Genotype 3: 63 \\
\hline
\textbf{POSITRON} & \\
Sofosbuvir plus ribavirin for 12 wk (\textit{n} = 207) & Genotype 2: 93 \\
& Genotype 3: 61 \\
Placebo for 12 wk (\textit{n} = 71) & Genotype 2: 0 \\
\hline
\textbf{FUSION} & \\
Sofosbuvir plus ribavirin for 12 wk (\textit{n} = 103) & Genotype 2: 82 \\
& Genotype 3: 30 \\
Sofosbuvir plus ribavirin for 16 wk (\textit{n} = 98) & Genotype 2: 89 \\
& Genotype 3: 62 \\
\hline
\textbf{NEUTRINO} & \\
Sofosbuvir plus ribavirin and peginterferon alfa & Overall for \\
for 12 wk (\textit{n} = 327) & genotypes 1 and 4–6: 90 \\
\hline
\end{tabular}
\caption{Percentage of Patients Achieving SVR12 in Sofosbuvir Phase III Trials\textsuperscript{19,20,a}}
\end{table}

\textsuperscript{a}SVR12 = sustained virological response, HCV = hepatitis C virus.
achieved SVR12 (95% CI, 86–93%; p < 0.0001). Most of the treatment failures in this study group could be attributed to relapse, with an overall relapse rate of 9%. The reported rate of SVR12 was impressive among a population largely composed of patients with HCV genotype 1 (89%). Since there were few subjects in the trial who were infected with HCV genotype 4, 5, or 6, conclusions regarding treatment of these genotypes with sofosbuvir plus ribavirin cannot be drawn.

Dosage recommendations

Simeprevir. Simeprevir should be administered at a dose of 150 mg once daily orally in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C virus genotype 1 for treatment-naïve patients or patients who have not responded to previous interferon-based therapy. For best results, simeprevir should always be taken with food. The dosage of simeprevir should never be reduced during therapy. Renal impairment of any degree does not warrant any dosage adjustments. No dosage recommendation is given for patients with moderate or severe hepatic impairment (Child–Pugh class B or C) due to the higher simeprevir exposure rates found in these patients.

Sofosbuvir. The recommended dosage of sofosbuvir is 400 mg once daily orally with ribavirin without regard to food for patients with HCV genotype 2 or 3. Unlike simeprevir and many of the historical treatments for HCV, sofosbuvir does not need to be taken in combination with peginterferon alfa-2a or alfa-2b when used in patients with HCV genotype 2 or 3. Peginterferon alfa-2a or alfa-2b should be used in combination with sofosbuvir and ribavirin when treating patients with HCV genotype 1 or 4. To ensure the most benefit from therapy, the dosage of sofosbuvir should not be reduced. No dosage adjustments are necessary in geriatric patients or in patients with mild-to-moderate renal impairment or mild, moderate, or severe hepatic impairment. In the absence of renal impairment, dosage adjustments are not necessary for patients with mild-to-moderate renal impairment or severe renal impairment. Studies have not been conducted to establish the safety of sofosbuvir in patients with end-stage renal disease, severe renal impairment, or decompensated cirrhosis. Sofosbuvir was used in combination with peginterferon plus ribavirin or ribavirin alone; however, when sofosbuvir was used with peginterferon alfa-2a or alfa-2b, nausea, insomnia, and anemia were common.

Drug interactions

Simeprevir. Simeprevir is a substrate of CYP3A4 and inhibits the organic anion-transporting polypeptide (OATP) 1B1/3 in the liver. Inhibition of OATP1B1/3 has been shown to increase rosuvastatin and atorvastatin concentrations. This interaction has warranted the creation of a maximum dose of both rosuvastatin and atorvastatin when taken with simeprevir. Moderate or strong CYP3A4 inhibitors (erythromycin and ritonavir) lead to increased concentrations of simeprevir. Decreased simeprevir concentrations were observed with moderate or strong CYP3A4 inducers (efavirenz and rifampin). Therefore, coadministration with moderate or strong CYP3A4 inducers or inhibitors is not recommended and should be avoided. Simeprevir inhibits intestinal CYP3A4, resulting in a drug–drug interaction with intravenous and oral midazolam. More information on the drug interactions associated with simeprevir is provided in the appendix.

Sofosbuvir. Sofosbuvir is a substrate of intestinal P-glycoprotein (Pgp). Decreased plasma concentrations of sofosbuvir were noted with potent Pgp inducers (e.g., rifampin, St. John’s wort) and should not be administered together. Inhibitors of Pgp (e.g., cyclosporine) may increase plasma concentrations of sofosbuvir, though no dosage adjustments are recommended. No clinically significant effects of sofosbuvir were seen with darunavir–ritonavir, emtricitabine, efavirenz, raltegravir, rilpivirine, tacrolimus, and tenofovir.

Adverse effects

Simeprevir. Common adverse effects of simeprevir include rash (photosensitivity), pruritus, nausea, myalgia, and dyspnea. Simeprevir was also associated with a mild-to-moderate increase in serum bilirubin concentrations that usually occurred early after treatment initiation and a slight increase in alkaline phosphatase levels.

Sofosbuvir. Headache and fatigue were reported frequently in patients receiving sofosbuvir in combination with peginterferon plus ribavirin or ribavirin alone; however, when sofosbuvir was used with peginterferon alfa-2a or alfa-2b, nausea, insomnia, and anemia were common.

Indications

Both simeprevir and sofosbuvir are approved for the treatment of chronic hepatitis C virus genotype 1 and other antiviral medications. Simeprevir has been approved specifically for patients infected with HCV genotype 1 with compensated liver disease (including cirrhosis) in combination with peginterferon alfa-2a or alfa-2b and ribavirin. It is strongly recommended that any patient considering therapy with simeprevir be screened at baseline for the NS3 Q80K polymorphism; if the polymorphism is present, alternative therapy options should be considered.

Sofosbuvir, on the other hand, has shown efficacy in HCV genotypes 1–4 and is approved by FDA for use in each. Sofosbuvir has also gained approval for patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HIV-1 coinfection.

Recommendations for retreatment of patients with HCV who have not responded to prior treatment have been published. 14

Place in therapy

Sofosbuvir is approved for the treatment of chronic hepatitis C virus genotype 1 and other antiviral medications. Simeprevir has been approved specifically for patients infected with HCV genotype 1 with compensated liver disease (including cirrhosis) in combination with peginterferon alfa-2a or alfa-2b and ribavirin. It is strongly recommended that any patient considering therapy with simeprevir be screened at baseline for the NS3 Q80K polymorphism; if the polymorphism is present, alternative therapy options should be considered.

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Recommendations for retreatment of patients with HCV who have not responded to prior treatment have been published. 14
Simeprevir and sofosbuvir

Cure means avoiding the possibility of curing a patient infected with HCV. A cure avoids the possibility of liver transplantation, which costs approximately $500,000. Earlier protease inhibitor–based regimens routinely cost $189,000 per course of therapy, achieved SVR of 64–75%, and carried a high risk of adverse events and associated costs.22

Conclusion

Simeprevir and sofosbuvir have advantages in response rates and convenient dosage forms and frequency compared with other HCV treatments; however, they are more expensive than previous HCV therapies.

References


Appendix—Drug–drug interactions associated with simeprevir

<table>
<thead>
<tr>
<th>Drug–Drug Interaction</th>
<th>Drug Categories and Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug increases simeprevir concentration</td>
<td>Antibiotics: erythromycin, clarithromycin, telithromycin</td>
</tr>
<tr>
<td></td>
<td>Antifungals: itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole</td>
</tr>
<tr>
<td></td>
<td>Herbal product: Milk thistle</td>
</tr>
<tr>
<td></td>
<td>HIV drugs: elvitegravir–cobicitabist–emtricitabine–tenofovir</td>
</tr>
<tr>
<td></td>
<td>Disoprolx fumarate, delavirdine, etravirine, nevirapine, darunavir–ritonavir, atazanavir, lopinavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir</td>
</tr>
<tr>
<td></td>
<td>Anticoagulants: warfarin, aspirin, clopidogrel, dabigatran</td>
</tr>
<tr>
<td></td>
<td>Antimycobacterial: clarithromycin, rifampin, rifabutin, rifampicin</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids: dexamethasone, prednisone</td>
</tr>
<tr>
<td></td>
<td>Herbal product: St. John’s wort</td>
</tr>
<tr>
<td></td>
<td>HIV drugs: stavudine, delavirdine, etravirine, nevirapine, atazanavir, lopinavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir</td>
</tr>
<tr>
<td></td>
<td>Antithyroid: propylthiouracil, methimazole</td>
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<tr>
<td></td>
<td>Statins: pravastatin, atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, rosuvastatin, simvastatin</td>
</tr>
<tr>
<td></td>
<td>Calcium-channel blockers: verapamil, diltiazem, felodipine</td>
</tr>
<tr>
<td></td>
<td>Calcium-channel blockers: verapamil, diltiazem, felodipine</td>
</tr>
<tr>
<td></td>
<td>Nifedipine, amiodarone, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil</td>
</tr>
</tbody>
</table>

*Simeprevir increases concentration of drug

| Drug decreases simeprevir concentration | Antibiotics: erythromycin, clarithromycin, telithromycin |
| | Antifungals: itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole |
| | Herbal product: Milk thistle |
| | HIV drugs: elvitegravir–cobicitabist–emtricitabine–tenofovir |
| | Disoprolx fumarate, delavirdine, etravirine, nevirapine, darunavir–ritonavir, atazanavir, lopinavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir |
| | Anticoagulants: warfarin, aspirin, clopidogrel, dabigatran |
| | Antimycobacterial: clarithromycin, rifampin, rifabutin, rifampicin |
| | Corticosteroids: dexamethasone, prednisone |
| | Herbal product: St. John’s wort |
| | HIV drugs: stavudine, delavirdine, etravirine, nevirapine, atazanavir, lopinavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir |
| | Antithyroid: propylthiouracil, methimazole |
| | Statins: pravastatin, atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, rosuvastatin, simvastatin |
| | Calcium-channel blockers: verapamil, diltiazem, felodipine |
| | Calcium-channel blockers: verapamil, diltiazem, felodipine |
| | Nifedipine, amiodarone, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil |

*Simeprevir decreases concentration of drug

*The drugs or herbal products listed are not recommended for use with simeprevir.


