Sofosbuvir in the Treatment of Chronic Hepatitis C: New Dog, New Tricks

George M. Abraham¹ and Linda M. Spooner²
¹Division of Infectious Diseases and Geographic Medicine, Department of Internal Medicine, Saint Vincent Hospital, University of Massachusetts Medical School; and ²Department of Pharmacy Practice, School of Pharmacy–Worcester/Manchester, MCPHS University, Worcester, Massachusetts

The existing standard of care for chronic hepatitis C virus (HCV) infection includes the use of pegylated interferon and ribavirin as primary components of treatment, with the addition of a direct-acting antiviral for genotype 1 infection. Sofosbuvir, an oral nucleotide inhibitor of the HCV nonstructural protein 5B RNA-dependent RNA polymerase enzyme, was recently approved for use in combination with ribavirin and/or pegylated interferon for chronic HCV infection, depending on the genotype. Sofosbuvir is orally administered, and peak plasma concentrations are not affected by food. The drug is renally eliminated and does not require adjustment in mild to moderate renal insufficiency or in any degree of hepatic impairment. Sofosbuvir is not metabolized by cytochrome P450 isoenzymes, nor does it induce or inhibit the metabolism of agents that are substrates of these enzymes. Sofosbuvir demonstrates a high barrier to resistance and was well tolerated by patients in clinical trials. Overall efficacy rates vary between 70% and 90%.

Keywords. sofosbuvir; hepatitis C; HCV.

Chronic hepatitis C virus (HCV) infection affects approximately 3.9 million people in the United States, and the disease resulted in >16,000 reported deaths in 2010 [1]. The highest death rates have been reported in people 55–64 years of age [1, 2], emphasizing the importance of detection and effective treatment of chronic HCV infection. The standard of care for all genotypes of HCV infection includes the use of pegylated interferon (peginterferon) and ribavirin (RBV) as primary components of treatment with the addition of a direct-acting antiviral for genotype 1 infection [3, 4]. Because of the many challenges that occur with the use of interferon-based regimens, including significant toxicities, administration issues, and suboptimal rates of sustained virologic response (SVR), there has been an impetus to develop newer agents with minimal adverse effects, more convenient administration (oral route), and improved chances of achieving SVR.

Sofosbuvir (SOF) is an oral nucleotide inhibitor of the HCV nonstructural protein 5B (NS5B) RNA-dependent RNA polymerase enzyme, and the agent demonstrates this activity across all genotypes of HCV [5]. It received approval from the US Food and Drug Administration (FDA) on 6 December 2013 for use in combination with RBV for genotypes 2 and 3 HCV infection or in combination with peginterferon and RBV for genotypes 1 and 4 infection [5]. Sofosbuvir can also be used in combination with RBV for patients with genotype 1 HCV infection who are ineligible to receive interferon treatment and for those patients with hepatocellular carcinoma resulting from chronic HCV infection who are awaiting transplant. Sofosbuvir is indicated for treatment of HCV infection in human immunodeficiency virus (HIV)–coinfected individuals [5]. Its approval is expected to dramatically enhance the management of HCV infection.

PHARMACOLOGY, PHARMACOKINETICS, AND RESISTANCE CONSIDERATIONS

As a uridine nucleotide prodrug, SOF is phosphorylated within hepatocytes via human cathepsin
Sofosbuvir is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) drug transporters. Drug interactions that may result from concomitant use with P-gp inducers will be discussed in the “Drug Interactions” section of this review. Sofosbuvir is not metabolized by cytochrome P450 isoenzymes, nor does it induce or inhibit the metabolism of agents that are substrates of these enzymes. Additionally, no dose adjustment is recommended for patients with any degree of hepatic impairment [5].

Sofosbuvir demonstrates a high barrier to resistance, as demonstrated by the lack of viral breakthrough experienced by patients in clinical trials, which will be discussed in detail in the “Clinical Trials” section of this review. In vitro studies have shown that the substitution of serine 282 with threonine (S282T) is the only resistance mutation that results in reduced susceptibility of HCV to SOF [7]. Because this mutation results in a reduction in the functional ability of the NS5B polymerase, it confers poor replicative capacity, a phenomenon also demonstrated by the absence of the S282T mutation in treatment-naive patients [8, 9]. Only 1 patient in clinical trials developed the S282T mutation; this occurred in a patient with genotype 2b infection who relapsed following treatment with SOF monotherapy, but the mutation was undetectable 12 weeks after completion of treatment [5, 10]. Additionally, SOF maintains activity against HCV with mutations conferring resistance to other classes of agents, including NS5B nonnucleoside inhibitors, nonstructural protein (NS) 5A inhibitors, and NS3/4A protease inhibitors [5].

**DRUG INTERACTIONS**

Sofosbuvir is a substrate, but not an inhibitor, of P-gp and BCRP; its metabolite GS-331007 is not a substrate of either protein [5]. Inducers or inhibitors of these transport proteins may affect SOF concentrations. Use of potent P-gp inducers, including St John’s wort, rifampin, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin with SOF should be avoided due to concerns of significant reductions in concentration and effectiveness of SOF. Tipranavir/ritonavir, rifabutin, and rifampin also decrease serum concentrations of SOF and should be avoided [5]. Cyclosporine increases SOF concentrations by 4.5-fold due to its inhibitory effects on P-gp and BCRP; however, as there was no clinically significant difference in adverse effects, no dose adjustment is required during concomitant use [11]. Sofosbuvir is neither a substrate nor an inhibitor of cytochrome 450 isoenzymes or uridine diphosphate glucuronosyltransferase 1A1. Studies combining SOF with darunavir/ritonavir, raltegravir, tenofovir, emtricitabine, efavirenz, rilpivirine, tacrolimus, and methadone demonstrated no significant drug interactions; thus, no dose adjustment is required with concomitant use of any of these agents [5].

**CLINICAL STUDIES**

The FDA’s approval of SOF is based on the results of 5 major trials, 4 of which were conducted in subjects with HCV genotype 2 or 3 infection; the major trials are summarized in Table 1 [12–15]. FISSION [12] evaluated SOF + RBV treatment for 12 weeks in treatment-naive subjects; POSITRON [13] evaluated SOF + RBV for 12 weeks in subjects who were interferon intolerant, ineligible, or unwilling to take interferon; FUSION [13] evaluated SOF + RBV for 12 or 16 weeks in treatment-experienced subjects (Table 2). VALENCE [14] evaluated genotype 2 or 3 infection in subjects who were either treatment naive or had not achieved an SVR with prior interferon-based treatment, and was originally designed as a 4:1 randomization to SOF vs placebo, but midway, based on emerging data, led to an unblinding of all subjects with all genotype 3 subjects being treated for 24 weeks with SOF + RBV (Table 1).

The NEUTRINO trial [12] evaluated SOF + peginterferon + RBV for 12 weeks in with HCV genotype 1, 4, 5 or 6 treatment-naive subjects (Table 2). The primary endpoint in all 4 phase 3 trials was SVR, defined as HCV RNA less than the lower limit of quantification 12 weeks after the discontinuation of active treatment. All SOF-containing arms used SOF 400 mg once daily and weight-based RBV (1000 or 1200 mg daily doses). These trials included a subset of subjects with compensated cirrhosis, a surrogate for a harder-to-treat subgroup.

The PHOTON-1 [15] trial evaluated HCV/HIV-coinfected patients with an all-oral regimen of SOF + RBV in varying durations (Table 3). Subjects with HIV were either not on treatment and had a CD4+ count >500 cells/µL or were virologically undetectable with a CD4+ count >200 cells/µL.
In addition, the FDA has granted approval of SOF in association with RBV to be used to treat patients with HCV genotype 1 who are monoinfected, for 24 weeks, if they are interferon unwilling, intolerant, or ineligible, albeit with lower response rates (76% vs 90%) [11].

More recently, the LONESTAR study [16] evaluated the use of SOF with ledipasvir (LDV) 90 mg, an NS5A inhibitor, that was used for either 8 or 12 weeks, and with or without RBV.

### Table 1. Summary of Major Comparative Studies of Sofosbuvir in Patients With Hepatitis C (Genotypes 2 and 3)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Comparator (No.)</th>
<th>Intervention (No.)</th>
<th>Virologic Efficacy (SVR&lt;sub&gt;12&lt;/sub&gt;)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relapse Rate&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>PEG/RBV (243)</td>
<td>SOF/RBV (256)</td>
<td>78% vs 95% (GT 2)</td>
<td>5% (4/73)&lt;sup&gt;c&lt;/sup&gt; vs 15% (9/62)</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td>Placebo&lt;sup&gt;d&lt;/sup&gt; (71)</td>
<td>SOF/RBV&lt;sup&gt;e&lt;/sup&gt; (207)</td>
<td>63% vs 56% (GT 3)</td>
<td>40% (72/179)&lt;sup&gt;f&lt;/sup&gt; vs 24% (37/155)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SOF/RBV&lt;sup&gt;i&lt;/sup&gt; (243) (12 wk)</td>
<td>SOF/RBV (256) (16 wk)</td>
<td>0% vs 93% (GT 2)</td>
<td>5% (5/107) vs n/a</td>
<td>[13]</td>
</tr>
<tr>
<td></td>
<td>(treatment-naive)</td>
<td>(GT 2 vs GT 3)</td>
<td>0% vs 61% (GT 3)</td>
<td>38% (37/98) vs n/a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(treatment-experienced)</td>
<td>(GT 2 vs GT 3)</td>
<td>84% (210/250) (GT 3)</td>
<td>10% (4/41)&lt;sup&gt;j&lt;/sup&gt; vs 20% (29/144)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** GT, genotype; n/a, not applicable; PEG, pegylated interferon alfa-2a; RBV, ribavirin; SOF, sofosbuvir; SVR<sub>12</sub>, sustained virologic response after 12 weeks.

<sup>a</sup> SOF + RBV arm with misclassified hepatitis C virus genotype. These subjects were excluded from analysis.

<sup>b</sup> Relapse rate at posttreatment week 12.

<sup>c</sup> Discontinuation rate due to an adverse event (AE): 1% in the SOF/RBV group vs 11% in the PEG/RBV group.

<sup>d</sup> Discontinuation rate due to an AE: 2% in the SOF/RBV group vs 4% in the PEG/RBV group.

<sup>e</sup> POSITRON study (interferon-intolerant, ineligible, unwilling).

<sup>f</sup> FUSION study (treatment experienced).

<sup>i</sup> VALENCE study (GT 2 for 12 weeks, GT 3 for 24 weeks).

<sup>j</sup> GT 2 vs GT 3 (treatment naive).

<sup>k</sup> GT 2 vs GT 3 (treatment experienced).

<sup>l</sup> Cirrhotic vs noncirrhotic.

### Table 2. Summary of Major Comparative Studies of Sofosbuvir in Patients With Hepatitis C (Genotypes 1, 4, 5, 6)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Intervention (No.)</th>
<th>Virologic Efficacy [95% CI]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>SOF/PEG/RBV (327)</td>
<td>90% [86%-93%]&lt;sup&gt;j&lt;/sup&gt; (295/327)</td>
<td>[12]&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>GT 1a/1b&lt;sup&gt;d&lt;/sup&gt;</td>
<td>89% [85%-93%]&lt;sup&gt;j&lt;/sup&gt; (261/292)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GT 1a</td>
<td>92% [87%-95%]&lt;sup&gt;j&lt;/sup&gt; (206/225)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GT 1b</td>
<td>82% [70%-90%]&lt;sup&gt;j&lt;/sup&gt; (54/66)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GT 4</td>
<td>96% [27%-28%] (27/28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GT 5</td>
<td>100% (1/1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GT 6</td>
<td>100% (6/6)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; GT, genotype; PEG, pegylated interferon alfa-2a; RBV, ribavirin; SOF, sofosbuvir; SVR<sub>12</sub>, sustained virologic response after 12 weeks.

<sup>a</sup> All who received at least 1 dose of study medication, based on the intention-to-treat principle, including 3 subjects in the SOF + RBV arm with misclassified hepatitis C virus genotype. These subjects were excluded from analysis.

<sup>b</sup> Overall rate.

<sup>c</sup> NEUTRINO study.

<sup>d</sup> Discontinuation rate due to an adverse event: <1% in both SOF/PEG/RBV groups.

**Table 3. Summary of Response Rates for Sofosbuvir-Based Therapy in Patients With Hepatitis C Virus (Genotypes 1, 2, 3)/HIV Coinfection**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Intervention (No.)</th>
<th>Virologic Efficacy (SVR&lt;sub&gt;12&lt;/sub&gt;)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relapse Rate&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>SOF/RBV GT 1 (114) (24 wk, treatment naive)</td>
<td>76% (87/114)</td>
<td>22% (25/113)</td>
<td>[15]&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>SOF/RBV GT 2 (26) (12 wk, treatment naive)</td>
<td>88% (23/26)</td>
<td>0% (0/25)</td>
<td>[15]</td>
</tr>
<tr>
<td>3</td>
<td>SOF/RBV GT 3 (13) (24 wk, treatment experienced)</td>
<td>92% (12/13)</td>
<td>8% (1/13)</td>
<td>[15]</td>
</tr>
</tbody>
</table>

**Abbreviations:** GT, genotype; HIV, human immunodeficiency virus; RBV, ribavirin; SOF, sofosbuvir; SVR<sub>12</sub>, sustained virologic response after 12 weeks.

<sup>a</sup> All who received at least 1 dose of study medication, based on the intention-to-treat principle, including 3 subjects in the SOF + RBV arm with misclassified hepatitis C virus genotype. These subjects were excluded from the analysis.

<sup>b</sup> Overall rate.

<sup>e</sup> PHOTON-1 study.
The triple combination of SOF + LDV + RBV for 8 weeks in treatment-naive patients had 100% response rates, as did a treatment with SOF + LDV + RBV for 12 weeks in treatment-experienced patients with/without cirrhosis. Other groups had almost similar response rates of 95% (given the number of subjects in each group were small).

COST CONSIDERATIONS

As with other treatment modalities employed in management of HCV infection, the pricing of SOF is a consideration with its use. The wholesale acquisition cost (WAC) of a 28-day supply of SOF is $28,000, thus resulting in a $1000 per-tablet price [16]. The WAC of a 12-week course of treatment with peginterferon, RBV, and SOF for a patient weighing >75 kg with genotype 1 infection is $96,715, and the actual acquisition price is even higher [17]. Prior authorization criteria have been, or are being, developed by insurance payers in an effort to promote cost-effective use of SOF. A recently published pharmacoeconomic analysis reported that SOF may be cost effective when used in place of boceprevir or telaprevir in treatment-naive patients with genotype 1 HCV infection [18]. In the future, additional pharmacoeconomic analyses should be performed to further quantify the cost of treatment vs complications (eg, hepatocellular carcinoma, liver transplant) that can occur if patients were to remain untreated.

ADVERSE EFFECTS

Overall, SOF was well tolerated by patients in clinical trials, illustrated by the 0%–4% overall discontinuation rate of SOF and RBV-containing regimens in phase 3 clinical trials [12, 13]. The most commonly reported adverse effects, occurring in >20% of patients, included fatigue and headache in patients who received SOF + RBV, and fatigue, headache, nausea, and insomnia in those who received SOF + RBV + peginterferon [5]. In the 3 comparative clinical trials, the overall incidence of grade 3 (severe) or higher adverse effects in groups treated with regimens containing SOF ranged from 7% to 8% in patients receiving 12 weeks of treatment and 4% in patients receiving 16 weeks of treatment [12, 13]. Only 1 patient died during these trials; the cause of death was attributed to intoxication with heroin and cocaine and was unlikely to be related to SOF treatment [11].

Ribavirin is well known to induce a hemolytic anemia; therefore, assessments of hematologic parameters were performed in clinical trials with SOF [12, 13]. The pooled analysis of the 3 comparative phase 3 trials of SOF + RBV combination regimens demonstrated an 8% overall rate of hemoglobin (Hb) <10 g/dL and <1% overall rate of Hb <8.5 g/dL [5]. When compared with the 14% rate of Hb <10 g/dL and 2% rate of Hb <8.5 g/dL observed in the peginterferon + RBV arm of the FISSION study, it is remarkable to note that the doses of RBV used were lower (800 mg/day) than those used in the SOF + RBV groups (1000 mg/day or 1200 mg/day) [12, 13]. Only 3 patients receiving SOF-containing regimens in phase 3 trials required a blood transfusion [11]. Additionally, no decrease in Hb was observed in patients receiving SOF monotherapy in the phase 2 ELECTRON trial [10]. Thus, SOF does not appear to worsen anemia when combined with RBV. In contrast to interferon-containing regimens, SOF + RBV did not decrease white blood cell or platelet counts [12, 13].

CONCLUSIONS

Sofosbuvir is the newest antiviral agent to be approved by the FDA and represents the first in a novel class of agents, an NS5B polymerase inhibitor, indicated in the treatment of chronic HCV infection in combination with RBV and with/without peginterferon. Infection with genotypes 1 and 4 can be treated with SOF/RBV/interferon for 12 weeks in treatment-naive/treatment-experienced/cirrhotic and pretransplant candidates, or SOF/RBV for 24 weeks in interferon-intolerant or unwilling patients, including HCV/HIV-coinfected patients. In patients with genotype 2 infection, 12 weeks of SOF + RBV achieves excellent response to therapy, whereas in patients with genotype 3 infection, 24 weeks of therapy seems to provide better results than 12 or 16 weeks. Table 4 summarizes the dosing and administration of SOF by genotype.

The adverse effect profile of SOF appears to be excellent, with no significant side effects compared with those of its companion therapy (RBV or interferon). It has a few drug–drug interactions that need to be kept in mind. Its safety in pregnancy and

Table 4. Dosing and Administration of Sofosbuvir in Hepatitis C Virus (HCV)–Monoinfected and HCV/HIV-Coinfected Individuals

<table>
<thead>
<tr>
<th>Patient Scenario</th>
<th>Treatment Regimen</th>
<th>Treatment Duration</th>
</tr>
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<tbody>
<tr>
<td>Genotype 1</td>
<td>SOF&lt;sup&gt;a&lt;/sup&gt; + PEG&lt;sup&gt;b&lt;/sup&gt; + RBV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12 wk</td>
</tr>
<tr>
<td>Genotype 1, interferon-ineligible&lt;sup&gt;d&lt;/sup&gt;</td>
<td>SOF&lt;sup&gt;a&lt;/sup&gt; + RBV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24 wk</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>SOF&lt;sup&gt;a&lt;/sup&gt; + RBV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12 wk</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>SOF&lt;sup&gt;a&lt;/sup&gt; + RBV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24 wk</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>SOF&lt;sup&gt;a&lt;/sup&gt; + PEG&lt;sup&gt;b&lt;/sup&gt; + RBV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12 wk</td>
</tr>
<tr>
<td>Patients with HCC awaiting liver transplant</td>
<td>SOF&lt;sup&gt;a&lt;/sup&gt; + RBV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Until transplant occurs/up to 48 wk</td>
</tr>
</tbody>
</table>

Abbreviations: HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; PEG, pegylated interferon alfa; RBV, ribavirin; SOF, sofosbuvir.

<sup>a</sup> SOF 400 mg by mouth once daily.

<sup>b</sup> PEG dosing is per individual prescribing information.

<sup>c</sup> RBV weight-based dosing: <75 kg, give 1000 mg by mouth in 2 divided doses; ≥75 kg, give 1200 mg by mouth in 2 divided doses.

<sup>d</sup> Intolerant, unwilling, or ineligible due to adverse effects.

Source: Gilead Sciences, Inc [5].
breastfeeding is not completely established yet. Resistance considerations are also not an issue, as the S282T mutation has not been observed to confer any significant fitness that would impact therapy. All in all, this drug appears to herald a new era in HCV therapy with the first chance to attempt treatment with an all-oral combination.

**Note**

**Potential conflicts of interest.** G. M. A. has received fees from Gilead Sciences, Inc. L. M. S. reports no potential conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**