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Sofosbuvir, a New Nucleotide Analogue, for the Treatment of Chronic Hepatitis C Infection

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Abstract

Objective: To evaluate the clinical role of sofosbuvir (Solvadi) in the treatment of hepatitis C virus (HCV). **Data Sources:** A MEDLINE, EMBASE, and Cochrane search indexed from January 2000 to July 2014 was performed using the search terms GS-7977 and sofosbuvir. **Study Selection and Data Extraction:** Studies including humans subjects, published in English, and assessing efficacy and safety of sofosbuvir in management of chronic HCV were evaluated. **Data Synthesis:** Sofosbuvir, a nucleotide analogue NS5B polymerase inhibitor, competes with nucleotides within the hepatocytes resulting in chain termination and inhibition of RNA replication. Trials evaluating the efficacy of sofosbuvir combination therapy have demonstrated significant advantage in sustained virologic response (SVR) over previous therapies. Genotype 1, 4, 5, and 6 patients treated with peginterferon-α, ribavirin, and sofosbuvir for 12 weeks achieved SVR rates of 90%. Twelve-week peginterferon-free regimens have resulted in SVR rates of 90% in genotype 2 patients, whereas genotype 3 patients required 24 weeks of therapy to achieve similar results. Favorable SVR rates were also seen in previously difficult-to-treat patient populations including cirrhosis, HIV coinfection, and treatment-experienced. Sofosbuvir appears to be well tolerated and relatively safe, avoiding severe adverse drug reactions, laboratory abnormalities, and resistance issues associated with traditional HCV therapies. The biggest limitation of sofosbuvir is the high cost associated with therapy. **Conclusions:** Sofosbuvir is a safe and effective treatment option for patients infected with genotypes 1 to 6 HCV including previously difficult-to-treat populations. The shorter duration, oral route, minimal side effects, and decreased resistance potential makes it a welcome addition to the treatment of chronic HCV.

Keywords

sofosbuvir, hepatitis C, infectious disease, gastroenterology, liver disease

Introduction

Hepatitis C virus (HCV) affects more than 3 million Americans, with less than half cognoscente of their diagnosis.[1,2] Up to 85% of patients infected will advance to chronic HCV and one third of those will develop cirrhosis or hepatocellular carcinoma.[2,3] Historically, treatment for chronic HCV included dual therapy with peginterferon-α and ribavirin; unfortunately, the numerous contraindications, adverse drug reactions (ADRs), long duration of therapy, and low rates of efficacy resulted in only 15% of patients undergoing therapy.[1-3] Historically, efficacy is defined as sustained virologic response (SVR) 6 months after therapy completion.[4] First introduced in the early 1990s, recombinant interferon-α monotherapy resulted in SVR rates of 15% to 20%.[4] The addition of ribavirin in the late 1990s increased SVR rates up to 38%, and the substitution of a pegylated interferon-α, in early 2000, increased rates to 40% for genotype 1 patients and 80% for genotypes 2 and 3.[4,5] This dual therapy was the standard of care for over a decade.

With the development of a HCV replication model in 1999 and more recently an infectious HCV isolate, the ability to develop new pharmacological agents has skyrocketed.[6] In 2011, therapy options for genotype 1 expanded with the approval of 2 oral directly active antiviral agents, telaprevir and boceprevir, used in combination with peginterferon-α and ribavirin.[3,5] This was a major advancement in therapy of previously difficult-to-treat genotype 1 disease with increased efficacy rates of 60% or higher.[4]

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Unfortunately, patients still experienced ADRs associated with dual therapy, with additional drug-specific effects including dysgeusia with boceprevir or rash and diarrhea with telaprevir.[1,5]

In late 2013, 2 new agents with activity against multiple HCV genotypes, simeprevir and sofosbuvir, were approved for the treatment HCV, with additional agents currently in the pipeline.[1,3] Given the rapidly evolving treatment options available, The Infectious Diseases Society of America, American Association for the Study of Liver Diseases, and the International Antiviral Society developed Web-based recommendations that can be quickly transformed based on new approvals and further study results.[1]

Sofosbuvir (Solvadi, Gilead, Foster City, CA) is a pangenotypic nucleotide analogue NS5B polymerase inhibitor that was approved by the Food and Drug Administration (FDA) in December 2013 for the treatment of HCV genotypes 1, 2, 3, and 4, including those with hepatocellular carcinoma awaiting liver transplant and those with HCV/HIV-1 coinfection.[3,7] A MEDLINE, EMBASE, and Cochrane search of the English language indexed from January 2000 to July 2014 was performed using the search terms GS-7977 and sofosbuvir. This article will focus on the current role of sofosbuvir in the treatment of chronic HCV.

Pharmacology and Pharmacokinetics

Sofosbuvir (GS-7977), a nucleotide analogue NS5B polymerase inhibitor, is a prodrug that is metabolized in the liver to its pharmacologically active form, uridine analogue triphosphate GS-461203, which is able to incorporate into the HCV RNA by NS5B polymerase resulting in termination of RNA synthesis ceasing viral replication.[7,8] Dephosphorylation results in formation of the nucleoside inactive metabolite GS-331007; although inactive, it is the primary product analyzed for pharmacokinetic data. Following oral administration, peak plasma concentration is seen within 0.5 to 2 hours postdose for sofosbuvir and within 2 to 4 hours for GS-331007.[7,8] Although administration of sofosbuvir with high-fat meals slowed the rate of absorption, there was little effect on drug concentration; thus, it can be taken without regard to meals.[7] Sofosbuvir is 61% to 65% bound to human plasma proteins and was found independent of drug concentration over the range of 1 μg/mL to 20 μg/mL, and the binding of GS-331007 was minimal.[8] Following a single dose of sofosbuvir, 80% was eliminated in the urine, with the majority (78%) recovered as GS-331007 and only 3.5% recovered as sofosbuvir. The pharmacokinetic profiles of sofosbuvir were similar in men and women, and neither race nor age (between 19 and 75 years) had a clinically significant effect on the exposure of sofosbuvir or its metabolite.[8]

Clinical Efficacy

Sofosbuvir has been evaluated in multiple phase 3 trials.[9-14] All trials employed the primary efficacy endpoint of sustained virologic response 12 weeks after completion of therapy (SVR12), defined as HCV RNA level below the lower limit of quantification. Based on analysis of pooled clinical trials, SVR12 was found to be a good indicator that response would be maintained until week 24 (SVR24); thus, SVR12 is suitable as a primary end point for regulatory approval.[15] Unless otherwise noted, the antiviral drugs and doses used in the trials include the following: sofosbuvir 400 mg by mouth once daily, ribavirin weight-based dosing (1000 mg per day in patients weighing <75 kg and 1200 mg per day in patients ≥75 kg) divided into 2 daily doses, and peginterferon-α alfa-2a (peginterferon-α; Pegasys, Roche) 180 μg subcutaneously once weekly.

Treatment-Naïve Patients in Combination With Peginterferon-α and Ribavirin

The NEUTRINO trial was a single-group, open-label trial of sofosbuvir plus peginterferon-α and ribavirin for 12 weeks in patients with HCV genotype 1, 4, 5, or 6 at sites within the United States.[9,10] The majority of patients in the trial had genotype 1 (89%) or 4 (9%), with a mean age of 52 years, 64% of the participants were male, 17% were black, and 17% had cirrhosis. Overall, a total of 295 of the 327 patients treated met the primary outcome of SVR12 (90%; 95% confidence interval [CI] = 87-93). When looking at specific genotypes, 89% of patients with genotype 1 and 96% of patients with genotype 4 disease achieved SVR12 (Table 1[9-14]). Although the sample sizes were small, all patients with genotypes 5 (n = 1) and 6 (n = 5) achieved SVR12. Multivariate logistic regression found that patients without cirrhosis had better SVR rates at 92% compared to patients with cirrhosis 80% (odds ratio [OR] = 3.9; 95% CI = 1.7-9.3; $P = .0018$), and patients with CC IL28B polymorphism (71%) had better response to therapy than those with non-CC IL28B genotype at 98% and 87%, respectively (OR = 8.0; 95% CI = 1.8-35.2; $P = .006$). This finding was not surprising since patients with the CC allele have historically demonstrated an improved response with interferon therapy.[9] All cases of virologic failure were due to relapse at end of treatment and no patients developed resistance to sofosbuvir. Therapy was well tolerated with only 2% of patients discontinuing therapy because of ADRs. Overall, this study shows that 12 weeks of therapy with sofosbuvir, peginterferon-α, and ribavirin in treatment-naïve patients with genotype 1, 4, 5, or 6 led to high rates of SVR12. Potential limitations in this study include a lack of a control group, lack of an assessment of medication adherence, and the small number of patients with genotype 5 or 6.

Table 1. Phase 3 Study Results[9-14].

HCV Genotype	Treatment History	Regimen	SVR12 Response Rates		Relapse Rate. % (n)
			Overall, % (n)	Cirrhosis, % (n)	
Genotype 1	Naïve (Neutrino)[9,10]	SOF + RBV + PEG-IFN × 12 weeks	89% (260/292)	81% (NR)	11% (32/292)
Genotype 2	Naïve (FISSION)[9,10]	SOF + RBV × 12 weeks	97% (69/73)	83% (10/12)	5% (4/73)
	Naïve or Intolerant (POSITRON)[11,12]	SOF + RBV × 12 weeks	93% (101/109)	94% (16/17)	5% (5/107)
	Experienced (FUSION)[11,12]	SOF + RBV × 12 weeks	86% (31/36)	60% (6/10)	18% (7/39)
		SOF + RBV × 16 weeks	94% (30/32)	78% (7/9)	11% (4/35)
	Naïve or Experienced (VALENCE)[13,14]	SOF + RBV × 12 weeks	93% (68/73)	82% (9/11)	7% (5/73)[a]
Genotype 3	Naïve (FISSION)[9,10]	SOF + RBV × 12 weeks	56% (102/183)	34% (13/38)	40% (72/179)
	Naïve or Intolerant (POSITRON)[11,12]	SOF + RBV × 12 weeks	61% (60/98)	21% (3/14)	38% (37/98)
	Experienced (FUSION)[11,12]	SOF + RBV × 12 weeks	30% (19/64)	19% (5/26)	66% (42/64)
		SOF + RBV × 16 weeks	62% (39/63)	61% (14/23)	38% (24/63)
	Naïve or Experienced (VALENCE)[13,14]	SOF + RBV × 24 weeks	84% (210/250)	68% (31/60)[b]	14% (34/249)[c]
Genotype 4	Naïve (Neutrino)[9,10]	SOF + RBV + PEG-IFN × 12 weeks	96% (27/28)	NR	4% (1/28)

Abbreviations: HCV, hepatitis C virus; SVR12, sustained virologic response 12 weeks after completion of therapy, defined as HCV RNA level below the lower limit of quantification; SOF, Sofosbuvir; RBV, Ribavirin; PEG-IFN, peginterferon-α; NR, not reported.
[a]Four patients that relapsed were treatment-experienced.
[b]Eighteen patients with cirrhosis that did not achieve SVR12 were treatment-experienced.
[c]Twenty-nine patients that relapsed were treatment-experienced.

Treatment-Naïve Genotypes 2 and 3 in Combination With Ribavirin

The FISSION trial was a randomized, active-control, non-inferiority study of sofosbuvir plus ribavirin for 12 weeks compared to standard of care peginterferon-α plus ribavirin 400 mg twice daily for 24 weeks in patients with genotype 2 (n = 55) or 3 (n = 359) HCV at multiple international sites.[9,10] Baseline demographics were similar between groups with 71% to 72% genotype 3, median age of 50 years, 66% were males, 3% were black, 20% had cirrhosis, and 43% had the CC IL28B allele. Overall results found that 67% of patients in both treatment arms achieved SVR12. A multivariate logistic regression analysis in patients receiving sofosbuvir found an overall enhanced success rate for patients with genotype 2 (97%) compared to genotype 3 (56%) (OR = 42.5; 95% CI = 9.5-189.2; $P < .0001$; Table 1[9-14]). Patients without cirrhosis had higher rates of SVR12 compared to those with cirrhosis, 72% versus 47%, respectively (OR = 2.9; 95% CI = 1.4-6.3; $P < .005$). Although not statistically significant, patients with the CC IL28B allele achieved better results than those without. Virologic relapse occurred in 74/83 patients that did not achieve SVR12, and further testing found no resistant mutations. One case of virologic breakthrough was reported during week 8 of therapy secondary to nonadherence. Overall, sofosbuvir was well tolerated with only 4% of patients withdrawing because of ADRs compared to 22% in the peginterferon-α arm. Sofosbuvir plus ribavirin was found to be noninferior to peginterferon-α plus ribavirin for treatment-naïve patients with genotypes 2 and 3. However, patients with genotype 3 or cirrhosis experienced lower rates of response. Potential limitations of the study include lack of medication adherence assessment and it was only powered to detect non-inferiority, questioning its potential role in the treatment of HCV.

Genotype 2 or 3 Treatment-Experienced or Unable to Tolerate Peginterferon-α Arm

Two phase 3 studies evaluated sofosbuvir plus ribavirin weight-based dosing in patients with genotype 2 or 3 HCV who had failed or were intolerant to peginterferon-α.[11,12] POSITRON was a 12-week, randomized, placebo-controlled, multisite international study in patients previously intolerant to, ineligible for, or uninterested in peginterferon-α. The baseline demographics were balanced between groups with a median age of 54 years, 54% were males, and 5% were black. The primary outcome of SVR12 was met in 78% (95% CI = 72-83) of patients receiving treatment (n = 207)

compared to 0% of patients receiving placebo (n = 71; $P <$ .0001). When analyzing specific genotypes, 93% of patients with genotype 2 infection (n = 109) met the primary outcome compared to only 61% of patients with genotype 3 infection (n = 98; Table 1[9-14]). All patients who achieved SVR12 also achieved SVR at week 24 post-therapy. There was no difference in response rates for genotype 2 patients with cirrhosis; however, only 21% of genotype 3 patients with cirrhosis achieved SVR12. All cases of virologic failure were due to relapse after therapy with no resistance mutations identified. Therapy was well tolerated with most patients experiencing only mild-moderate ADRs, and only 2% of patients withdrawing secondary to ADRs compared to 4% in the placebo group. Potential limitations include small percentage of blacks, mechanism to validate patient adherence to therapy, and lack of a treatment comparator arm.

Patients with genotype 2 or 3 HCV that had previously failed peginterferon-α therapy were evaluated in the FUSION trial, a blinded, active-control, multisite international study.[11,12] Patients were randomized to receive sofosbuvir and ribavirin weight-based dosing for 12 (n = 103) or 16 weeks (n = 98). Baseline demographics were similar between groups with a median age of 56, 70% were male, 3% were black, and 75% had relapsed with interferon therapy. The primary outcome, SVR12, was achieved in 50% (95% CI = 40-60) of patients in the 12-week arm and 73% (95% CI = 63-81) of patients in the 16-week arm ($P <$ .001). Consistent with previous trials, genotype 2 patients achieved high rates of SVR12 regardless of duration (86% to 94%; Table 1[9-14]). However, increasing duration of therapy from 12 to 16 weeks in genotype 3 patients doubled the rates of SVR12 up to 62%, including those with cirrhosis. All cases of virologic failure (n = 76) were due to relapse posttreatment, and further analysis found no resistance present. Most ADRs were consistent with ribavirin toxicity and caused only 1 patient to discontinue therapy. The POSITRON and FUSION studies found that 12 weeks of sofosbuvir plus ribavirin was efficacious in patients with genotype 2 or 3 HCV regardless of previous treatment status. Extending therapy duration to 16 weeks, as was done in the POSITRON trial, had the greatest impact on genotype 3 patients and those with cirrhosis. Potential limitations include small number of blacks and patients with cirrhosis and lack of medication adherence validation.

The VALENCE trial evaluated sofosbuvir and ribavirin weight-based dosing in patients with genotype 2 or 3 HCV regardless of previous treatment status.[13,14] Based on evidence showing increased efficacy in genotype 3 patients with durations greater than 12 weeks, the initial protocol was amended to extend treatment in this group to 24 weeks. The study terminated the placebo arm and was redefined as an unblinded descriptive study removing all hypothesis testing. Baseline demographics were similar between groups with a median age of 51 years, 60% were males, and 7% were black. One interesting finding was that all black patients included had genotype 2 disease. The primary outcome of SVR12 was achieved in 93% of patients (n = 73) with genotype 2 HCV (95% CI = 85-98) and in 85% of patients with genotype 3 (n = 250; 95% CI = 80-89; Table 1[9-14]). Previous treatment status had minimal effect on SVR12 rates in the genotype 2 cohort; however, treatment-experienced genotype 3 patients had poorer response rates compared to treatment-naïve patients, 94% and 79%, respectively. Genotype 3 patients with cirrhosis also had lower response rates compared to noncirrhotic patients (68% and 91%, respectively). A further analysis found that 4 factors were associated with SVR12 in genotype 3 patients: baseline HCV RNA level <6 $\log_{10}$ IU per mL, female sex, absence of cirrhosis, and age less than 50 years. One patient experienced virologic breakthrough during therapy secondary to nonadherence, and all other cases (n = 42) were secondary to relapse after completion of therapy and no resistant variants were identified. Adverse effects were similar between the 12- and 24-week treatment groups, with only 1% of patients in each arm discontinuing therapy secondary to ADRs. A potential limitation of this study is the small sample of black patients included, lack of medication adherence validation, and the lack of formal statistical comparisons due to the study redesign. Overall, this study shows that extending therapy to 24 weeks for genotype 3 patients results in higher rates of SVR12 without reducing its tolerability.

Genotype 1 Dual Direct Acting Antiviral Therapy

Sofosbuvir has been tested with other direct-acting antiviral agents with and without ribavirin. The COSMOS study is a phase 2, open-label, trial investigating sofosbuvir plus simeprevir 150 mg daily (NS3/4A protease inhibitor) with or without weight-based ribavirin for 12 or 24 weeks in patients with genotype 1 HCV.[16-18] The trial was divided into 2 cohorts and is only available in abstract form. Cohort 1 (n = 80) evaluated previous null responders with mild fibrosis.[16,17] SVR12 was achieved in 93% (13/14) of patients in the 12-week group and all patients (13/13) in the 24-week group. The addition of ribavirin had minimal impact on SVR rates. Cohort 2 (n = 82) evaluated treatment-naïve or previous null responders with advanced fibrosis/cirrhosis.[15,17] Overall, SVR12 was achieved in greater than or equal to 93% (82/87) of patients regardless of duration or concomitant ribavirin. Adverse effects in both cohorts were similar between groups regardless of treatment duration or ribavirin use, and only 4 patients discontinued therapy due to ADRs.[15-17] The increase in bilirubin associated with simeprevir was common but mild in severity. Unfortunately, this study is available in abstract form only, and further evaluation after full publication will be needed.

Table 2. American Association for the Study of Liver Disease, the Infectious Diseases Society of America, and the International Antiviral Society-USA. Recommendations for Testing, Management, and Treating Hepatitis C[1].

Genotype	Interferon Eligibility	Preferred	Alternative
Genotype 1	Eligible	SOF + weight-based RBV + PEG-IFN × 12 weeks	SMV x 12 weeks + weight-based RBV + PEG-IFN × 24 weeks[a]
	Not Eligible	SOF + SMV ± weight-based RBV × 12 weeks	SOF + weight-based RBV × 24 weeks[b]
Genotype 2		SOF + weight-based RBV × 12 weeks	none
Genotype 3		SOF + weight-based RBV × 24 weeks	SOF + weight-based RBV + PEG-IFN × 12 weeks
Genotype 4	Eligible	SOF + weight-based RBV + PEG-IFN × 12 weeks	SMV + weight-based RBV + PEG-IFN × 24-48 weeks
	Not Eligible	SOF + weight-based RBV × 24 weeks	none
Genotype 5 or 6	Eligible	SOF + weight-based RBV + PEG-IFN × 12 weeks	Weight-based RBV + PEG IFN × 48 weeks

Abbreviations: SOF, sofosbuvir 400 mg by mouth once daily; Weight-based RBV, ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) by mouth in divided doses twice daily); PEG-IFN, peginterferon-α 180 µg subcutaneously; SMV, simeprevir 150 mg by mouth daily.
[a]Patient should have genotype 1b or 1a without Q80K polymorphism detected.
[b]Preliminary data show to be less effective alternative, especially among cirrhotic patients.

Daclatasvir is an HCV NS5B replication complex inhibitor.[19] A phase 2, open-label study evaluated the efficacy of daclatasvir 60 mg once daily plus sofosbuvir with or without weight-based ribavirin for 12 to 24 weeks in treatment-naïve genotype 1, 2, or 3 patients and in genotype 1 patients that failed to achieve a response with telaprevir or boceprevir. Overall, 98% of treatment-naïve genotype 1 (n = 126), 92% of genotype 2 (n = 26), and 89% of genotype 3 (n = 18) patients achieved the primary outcome of SVR12. Of the 41 genotype 1 patients that had failed previous protease inhibitor therapy, 40 attained SVR12 (98%). There was no major difference for SVR12 attainment based on duration of therapy, specific genotype, IL28B genotype, or ribavirin use during therapy. This study shows that once daily dosing of daclatasvir plus sofosbuvir for 12 to 24 weeks in treatment-naïve or 24 weeks in treatment-experienced was associated with high rates of SVR12 regardless of ribavirin use. Phase 3 studies are currently ongoing to further justify the efficacy and safety of this combination. The data for both simeprevir and daclatasvir help solidify the possibility of all-oral, ribavirin-free regimens that are efficacious for multiple genotypes.

Ledipasvir is an HCV NS5A inhibitor that has shown potent antiviral activity against genotype 1 HCV.[20-22] Multiple phase 2 trials of sofosbuvir plus ledipasvir with or without ribavirin for 8 to 12 weeks in treatment-naïve and for 12 weeks in patients that had failed a prior protease inhibitor resulted in SVR12 rates of greater than 90%.[20,21] A recent phase 3 study involving treatment-naïve genotype 1 patients without cirrhosis (n = 647) was completed to determine if shortening therapy to 8 weeks with or without ribavirin affected SVR12 rates compared to 12 weeks of ledipasvir 90 mg plus sofosbuvir alone.[22] This was a randomized, open-label trial occurring at multiple sites in the United States. SVR12 was achieved by 94% of patients in the 8-week ledipasvir and sofosbuvir group (n = 215), 93% of patients in the 8-week ledipasvir and sofosbuvir plus ribavirin group (n = 216), and 95% of patients in the 12-week ledipasvir and sofosbuvir group (n = 216). No patient experienced virologic failure during treatment, and all virologic failures occurred as relapse after end of treatment. Secondary noninferiority outcome analysis shows that 8 weeks of ledipasvir and sofosbuvir was noninferior to 12 weeks of therapy or 8 weeks with ribavirin. Adverse effects were lower for the ribavirin-free regimens at 67% to 69% compared to 76% for the ribavirin-containing arm, and only 3 patients withdrew from the study because of ADRs. This study highlights the ability to develop an oral regimen that is shorter in duration compared to the previous standard of treatment with similar efficacy and lower occurrence of ADRs.

Dosing and Administration

Based on its pharmacokinetic profile, sofosbuvir is dosed 400 mg by mouth daily regardless of HCV genotype.[7-9] Concomitant treatment and duration of 12 to 24 weeks is dependent on HCV genotype and previous treatment attempts (Table 2). Sofosbuvir can be given without regard to food.[7,8] Sofosbuvir has not been studied in patients less than 18 years of age.[7] Based on studies in patients more than 65 years, no dosage adjustment is recommended. No dose adjustment is needed for patients with mild-moderate renal impairment; however, the safety and efficacy have not been evaluated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or with end-stage renal disease requiring hemodialysis.[7] No dosage adjustments are

Table 3. Special Population Study Results[23-26].

Special Population	Patient Characteristics	Regimen	SVR12 Response Rates, % (n)	Posttreatment Relapse Rate, % (n)
Liver transplant[23]		SOF + RBV × 12 weeks	64% (25/39)	10/38
HIV coinfection[24-26]	Genotype 1, Treatment-Naïve	SOF + RBV × 24 weeks	76% (87/114)	22% (25/113)
	Genotype 2, Treatment-Naïve	SOF + RBV × 12 weeks	88% (23/26)	0/26
	Genotype 2, Treatment-Experienced	SOF + RBV × 24 weeks	92% (22/24)	4% (1/24)
	Genotype 3, Treatment-Naïve	SOF + RBV ×12 weeks	67% (28/42)	29% (12/42)
	Genotype 3, Treatment-Experienced	SOF + RBV × 24 weeks	94% (22/24)	6% (1/24)

Abbreviations: HCV, hepatitis C virus; GT, genotype; SVR12, sustained virologic response 12 weeks after completion of therapy, defined as HCV RNA level below the lower limit of quantification; SOF, sofosbuvir; RBV, ribavirin; PEG-IFN, peginterferon-α.

needed for patients with Child-Pugh Class A, B, or C liver disease; hepatic impairment, or cirrhosis.

Special Populations

Patients Awaiting Liver Transplantation

The suppression of HCV titers prior to liver transplantation can decrease risk of recurrence. Sofosbuvir plus ribavirin weight-based dosing was evaluated in 61 patients with hepatocellular carcinoma awaiting liver transplant.[23] The median age was 49 years, 80% were male, and 72% had genotype 1 disease. A total of 93% (41/44) of patients had SVR at time of transplant, and 64% (25/39) of patients achieved SVR 12 weeks after liver transplantation (Table 3[23-26]). Continuous number of days that HCV was not detected prior to transplant was the only factor associated with HCV recurrence; only 1 out of 24 patients with greater than 30 days of undetectable HCV RNA experienced recurrence compared to 9 out of 14 with less than 30 days. Overall, therapy was well tolerated, and only 2 people withdrew from therapy because of ADRs not related to sofosbuvir. There are currently no recommendations on the use of sofosbuvir in patients post-transplant.

HIV/HCV Coinfection

Sofosbuvir has also been evaluated in patients coinfected with HIV. The PHOTON-1 trial was an open-label trial of sofosbuvir plus weight-based ribavirin in genotype 1, 2, and 3 HCV patients coinfected with HIV and has only been published in abstract form.[7,24-26] Approximately 85% of patients were male with a mean age of 50 years.[26] One third of patients with genotype 1 (n = 114) were black and 22% had IL28B CC allele, whereas 15% of patients with genotypes 2 and 3 (n = 109) were black and 42% had the IL28B CC allele. A majority of patients (95%) were receiving antiretroviral therapy (ART) at initiation, with an undetectable HIV RNA and CD4 counts greater than 200 cells/mm^3.[7,24-26] The other 5% of patients were not on therapy, with CD4 counts greater than 500 cells/mm^3. All genotype 1 patients were HCV treatment-naïve and received therapy for a total of 24 weeks (n = 114). Genotype 2 and 3 patients could be either treatment-naïve or experienced. Treatment duration was 12 weeks for patients that were treatment-naïve (n = 68) and 24 weeks for patients that were treatment-experienced (n = 28). A total of 76% of patients with genotype 1 HCV achieved SVR12 (Table 3[23-26]). Twelve weeks of therapy for treatment-naïve patients led to SVR12 rates of 88% for genotype 2 and 67% for genotype 3. Twenty-four weeks of therapy for treatment-experienced patients led to SVR12 rates of 92% and 94%, respectively. All virologic failure in the treatment-naïve population was due to relapse, except for 2 that were secondary to nonadherence.[26] No evidence of resistant alleles was found in patients that relapsed. Overall, therapy was fairly tolerable with ADRs consistent with ribavirin. A majority of patients completed therapy (90% to 98%), with only 2% to 4% discontinuing because of ADRs. This study demonstrates that an all-oral, non-interferon-based regimen with sofosbuvir plus ribavirin leads to high rates of SVR12 in HCV patients coinfected with HIV that are comparable to patients that are not coinfected with HIV. Further analysis found sofosbuvir safe to use with ART and lacks many of the drug interactions commonly seen with boceprevir and telaprevir. Sofosbuvir had no negative effects on HIV suppression or CD4 counts.

Pregnancy and Lactation

Sofosbuvir has not been evaluated in pregnancy; however, ribavirin is considered a pregnancy category X medication and is contraindicated in women who are or may become pregnant.[7,27,28] Women of childbearing potential and their male partner should not receive ribavirin without using 2 forms of reliable birth control during treatment and a minimum 6 months thereafter; patients should also undergo monthly pregnancy tests.[7,28] Sofosbuvir has not been studied in nursing mothers.[7] GS-331007 was the primary metabolite found in milk of lactating rats, although no effect was seen on the nursing pups, the risk versus benefit of

therapy in a breastfeeding mother as well as concomitant use with ribavirin will have to be assessed.

Adverse Effects/Safety

Throughout published trials, the overall discontinuation rate of sofosbuvir is low, ranging from 0% to 2.4%.[7-14] Reported ADRs are likely attributable to well-known adverse effects of ribavirin and peginterferon-α. Commonly reported ADRs (>20% patients) in patients taking sofosbuvir plus ribavirin were headache and fatigue; when peginterferon-α was added to therapy, nausea, insomnia, and anemia were also reported. At this time, no concerning ADRs have been identified and sofosbuvir seems to be well tolerated.

Drug Interactions

Sofosbuvir is a substrate of transporter P-glycoprotein; however, neither sofosbuvir nor GS331007 is a substrate for or induce CYP450 enzymes.[7,8,29-31] Evidence shows that concomitant use with p-glycoprotein inducers (carbamazepine, phenytoin, phenobarbital, and oxcarbazepine, rifaputin, rifampin, rifapentine, St. John's wort, tipranavir, and ritonavir) will lead to decreased levels of sofosbuvir and the active metabolite GS-331007, thus leading to a decreased therapeutic effect of sofosbuvir. Coadministration with these agents is not recommended.

Resistance

In vitro testing to appraise the resistance profile of sofosbuvir in HCV genotypes 1 to 6 found the NS5B S282T variant to be the sole mutation that is associated with reduced susceptibility to sofosbuvir.[32] To this point, the S282T mutation has not been identified clinically among patients who experienced virologic relapse after completing a course of sofosbuvir.[7] Additional variants were also observed; however, none of these were associated with decreased susceptibility of sofosbuvir.[32] The clinical significance of the primary S282T mutation and the other substitutions are unknown at this time, but sofosbuvir appears to have a high threshold for resistance development.[7]

Cost Issues

While sofosbuvir addresses many treatment barriers, one will likely remain: cost. The current wholesaler acquisition cost in the United States is $1000 per tablet or $84 000 for a 12-week treatment course.[33] Additional costs will include ribavirin or peginterferon-α, which can cost anywhere between $15 000 and $30 000 depending on duration of treatment.[34] One recent cost-effectiveness analysis estimated a 24-week course of sofosbuvir plus ribavirin to cost about $169 000 and 12 weeks of simeprevir plus sofosbuvir to cost around $150 000.[35] While many clinicians, insurance companies, and patients experience sticker shock with these price estimates, it is important to consider the cost implications of curing patients with HCV. It is estimated that treatment with previous standard of care, peginterferon-α and ribavirin combination therapy, resulted in total direct medical costs averaging $28 547 per year with outpatient pharmacy costs typically estimating $17 419.[36] Though costs of previous standard care are much lower than the costs of HCV treatment utilizing sofosbuvir, the decreased duration of therapy, minimal ADRs and lab monitoring, and improved SVR rates achieved with sofosbuvir will greatly increase the number of patients successfully completing therapy. While there will be an initial increase in drug costs, the long-term benefits of curing HCV and preventing disease progression are still unseen.

Conclusion

Sofosbuvir is a new nucleotide analogue NS5B polymerase inhibitor indicated for the treatment of chronic HCV. The approval of sofosbuvir for the treatment of genotypes 1 to 4 expands options and ability to cure patients with HCV. The lack of contraindications to therapy, potential all-oral regimens, and minimal ADRs and drug interactions will add to the quality of life of our patients. Genotype 1 is the most common cause of HCV in the United States, and unfortunately, combination treatment with peginterferon-α, ribavirin plus sofosbuvir is still the preferred therapy.[3] However, the addition of sofosbuvir decreases the duration of therapy to 12 weeks and results in SVR12 in almost 90% of patients treated, regardless of their cirrhosis and CC IL28B status.[9,10] The future holds many possibilities for genotype 1 patients including potential all-oral regimens with soon-to-be approved direct-acting antiviral agents, removing the contraindications and ADRs associated with peginterferon-α.

Patients with genotype 2 HCV had overwhelmingly positive results showing that sofosbuvir plus ribavirin for 12 weeks led to SVR12 rates of greater than 90% in treatment-naïve patients, with similar results seen in treatment-experienced patients.[11-14] Extending the duration of therapy to 16 weeks may be beneficial in treatment-experienced patients with cirrhosis; however, the sample size was small so further research is needed to come to a definite conclusion.[11,12]

Unfortunately, SVR rates are consistently lower for genotype 3 patients.[9-14] Like genotype 2 patients, genotype 3 patients have the option for a peginterferon-α-free regimen; however, studies have shown better results with an extended duration of therapy. Initial 12-week studies of sofosbuvir plus ribavirin resulted in efficacy rates of 55% to 60% for treatment-naïve and 30% for treatment-experienced.[9-12] Extending the duration of therapy to 24 weeks increased

efficacy rates to greater than 80% in patients without cirrhosis and almost 70% in patients with cirrhosis.[13,14] A majority of patients with cirrhosis that relapsed were treatment-experienced.

A major limitation of the current sofosbuvir data is the lack of results for genotype 4, 5, and 6 HCV.[9,10] However, the small sample sizes found within the trials is consistent with the prevalence of these genotypes in the United States.[1-3] The phase 3 trial data that are available are promising, with 33/34 patients achieving SVR12 with sofosbuvir plus peginterferon-α and ribavirin.[9,10]

The addition of sofosbuvir expands the potential for patients who previously had very limited therapy options due to factors associated with poorer SVR outcomes: cirrhosis, black race, and non-CC IL28B genotype.[1,3] Based on the data presented, it is evident that patients treated prior to developing cirrhosis benefit the most, whereas race and ethnicity had minimal impact on efficacy. As expected, patients with the CC IL28B genotype experienced improved rates of response with interferon-free regimens; however, patients with non-CC IL28B had promising results with the all-oral regimens. The adverse events seen in these studies were consistent with those seen in patients treated with peginterferon-α or ribavirin, with approximately 1% of patients discontinuing therapy because of ADRs. The absence of the S282T mutation gene in patients treated with sofosbuvir is a welcome change to the emergence of resistance associated with other antiviral agents. Overall, these studies show that sofosbuvir improves SVR12 compared to traditional regimens regardless of genotype. Further studies looking at ribavirin-free regimens are ongoing, and changes to the current recommendations are expected as further information is discovered.

Declaration of Conflicting Interests

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