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REVIEW

Sofosbuvir treatment and hepatitis C virus infection

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Abstract

Hepatitis C virus (HCV) infection is a serious problem worldwide. The use of interferon-based therapy has made HCV eradication challenging. The recent appearance of direct-acting antiviral agents (DAAs) has changed HCV therapy. Combining the use of DAAs with peginterferon and ribavirin has improved treatment efficacy. Furthermore, the combination of different orally administered DAAs has enabled interferon-free therapy with much higher efficacy and safety. In particular, sofosbuvir, a nucleotide-based NS5B inhibitor, prevents HCV RNA synthesis by acting as a "chain terminator". Treatment with sofosbuvir has attained an extremely high rate of sustained virologic response. The current review summarizes the efficacy and safety of sofosbuvir therapy.

Key words: Hepatitis C virus; Interferon; Interferon-free; Genotype; Sofosbuvir

Core tip: Sofosbuvir, a nucleotide-based NS5B inhibitor, is an effective treatment against pangenotypic strains of hepatitis C virus (HCV). Sofosbuvir-containing regimens have attained extremely high rates of sustained virologic response. Because regimens including sofosbuvir result in fewer adverse events than interferon-based regimens, sofosbuvir has taken a central role in HCV treatment.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a global public health problem. Approximately 130 to 170 million people experience chronic HCV infection, which has a global prevalence of 2%-3%[1,2]. In 2002, worldwide, 27% of 783000 deaths from cirrhosis and 25% of 619000 deaths from hepatocellular carcinoma were attributed to HCV infection[3].

The use of interferon-based therapy has made HCV eradication challenging, especially for patients infected with HCV genotype 1. Treatment with peginterferon plus ribavirin induces only about 50% of patients infected with HCV genotype 1 at high viral loads to achieve sustained virologic response (SVR)[4], while about 80% of patients infected with HCV genotypes 2 and 3 achieve SVR[5].

The appearance of direct-acting antiviral agents (DAAs), which specifically target HCV proteins, has provided insights into the current situation. The use of protease inhibitors, such as telaprevir, boceprevir, simeprevir, faldaprevir and vaniprevir, in combination with peginterferon and ribavirin has improved treatment efficacy in treatment-naïve patients (70% to 80% achieve SVR) and in patients infected with HCV genotype 1 who have relapsed post-treatment[6-10]. However, SVR rates in patients who exhibited no responses to previous treatments remain low[11,12]. Furthermore, patients who are ineligible for or intolerant to treatment with peginterferon plus ribavirin are contra-indicated from receiving the above treatment.

The use of combinations of different orally administered DAAs has enabled the realization of interferon-free therapy. DAA-based therapies generally have higher treatment efficacy and lower risk for adverse effects compared to regimens using interferon. In particular, sofosbuvir, a pyrimidine nucleoside analog inhibitor of HCV pangenotype NS5B polymerase, has produced extremely high rates of SVR when used in combination with other DAAs. In the current review, we discuss the use of treatment regimens that include sofosbuvir to combat HCV.

STRUCTURE OF HCV GENOME AND DAAS

HCV is an enveloped, positive-stranded RNA virus. Its genome spans 9600 nucleotides in length and contains a 5′ non-translated region (5′ NTR), a single open reading frame and a 3′ NTR. A single polyprotein is translated from HCV genome and is then cleaved into structural (core, E1, E2 and p7) and non-structural (NS2, NS3, NS4A, NS4B, NS5A and NS5B) proteins[4]. The serine protease NS3 plays a key role in processing the HCV polyprotein. The phosphoprotein NS5A and RNA-dependent RNA polymerase NS5B are essential to the replication of HCV RNA. DAAs against HCV target these proteins and strongly inhibit HCV replication.

The first-generation NS3/4A protease inhibitors telaprevir and boceprevir are typically used in combination with peginterferon and ribavirin. This triple regimen has improved SVR rates in HCV genotype 1-infected patients[6,7] but often produces serious adverse events[13]. The second-generation NS3/4A protease inhibitors simeprevir, faldaprevir and vaniprevir have further improved treatment efficacy while resulting in fewer adverse effects[8-10].

In Japan, daclatasvir, a first-in-class NS5A inhibitor, enabled effective interferon-free therapy for the first time. Interferon-free dual oral therapy with daclatasvir and asunaprevir, a NS3/4A protease inhibitor, led to high SVR rates (87.4% in interferon-ineligible or -intolerant patients, 80.5% in non-responders, 89.1% in treatment-naïve patients, and 95.5% in relapsers)[14,15]. However, the evolution of drug-resistant HCV variants has created new problems. For example, Y93H variants of the NS5A protein have markedly decreased SVR rates to as low as 43.3%[14].

Sofosbuvir

Sofosbuvir (formerly known as GS-7977; Gilead Sciences, Foster City, CA, United States) is a nucleotide NS5B inhibitor[16]. Sofosbuvir is converted into a pharmacologically active form (GS-461203) within hepatocytes[17]. GS-461203 inhibits RNA-dependent RNA polymerase activity by competing with uridine and prevents HCV RNA synthesis by acting as "chain terminator". Because the catalytic site of the NS5B protein is highly conserved, sofosbuvir is believed to have pangenotypic activity[18].

Another favorable characteristic of sofosbuvir is its high genetic barrier. In an HCV replicon study, a S282T substitution in NS5B was reported to impart drug resistance[19]. However, in clinical trials, this NS5B variant was detected in only one patient after treatment with sofosbuvir monotherapy[16,20-22]. Foster *et al*[23] reported that sofosbuvir treatment led to the emergence of drug-resistant variants in 9/78 (12%) of patients. An L159F variant was present both at baseline and at the time of virologic failure in 1 patient and at the time of virologic failure in 7 additional patients. The V321A variant emerged at the time of virologic failure in 2 patients.

Sofosbuvir also possess a noteworthy safety profile and high tolerability. In phase 3 trials of sofosbuvir, the frequency of serious adverse events ranged from 1% to 8% and the rate of treatment discontinuation because of adverse events range from 0% to 4.4%[24,25].

CLINICAL EFFICACY OF TREATMENT REGIMEN CONTAINING SOFOSBUVIR

More than 3000 patients have been assessed in clinical

Table 1 Summary of phase 3 study for hepatitis C virus genotype 1-infected patients

Study name	Population	Treatment	Duration (wk)	*n*	LC (%)	SVR12 (%)		
						All	Non-LC	LC
NEUTRINO	Naïve	SOF/PEG-IFN/RBV	12	291	-	89	-	81
ION-1	Naïve	SOF/LDV	12	210	16	99	100	97
		SOF/LDV/RBV	12	216	15	97	97	100
		SOF/LDV	24	214	15	98	99	97
		SOF/LDV/RBV	24	214	17	99	99	100
ION-3	Naïve	SOF/LDV	8	214	0	94	94	-
		SOF/LDV/RBV	8	216	0	93	93	-
		SOF/LDV	12	216	0	95	95	-
Japanese study	Naïve	SOF/LDV	12	83	16	100	100	100
		SOF/LDV/RBV	12	83	14	96	97	92
ION-2	Experienced	SOF/LDV	12	20	94	95	86	20
		SOF/LDV/RBV	12	20	96	100	82	20
		SOF/LDV	24	20	99	99	100	20
		SOF/LDV/RBV	24	20	99	99	100	20
Japanese study	Experienced	SOF/LDV	12	32	100	100	100	32
		SOF/LDV/RBV	12	25	100	100	100	25

LC: Liver cirrhosis; SVR12: Sustained virologic response at 12 wk; Naïve: Treatment-naïve; Experienced: Treatment-experienced; SOF: Sofosbuvir; LDV: Ledipasvir; PEG-IFN: Peginterferon; RBV: Ribavirin.

studies of treatment regimens containing sofosbuvir. Below, we describe the efficacy of a sofosbuvir-containing regimen.

HCV genotype 1-specific virologic response of sofosbuvir

The results from phase 3 clinical trials evaluating the use of treatment regimens containing sofosbuvir against HCV genotype 1 are shown in Table 1. The NEUTRINO study was the first phase 3 trial to evaluate sofosbuvir-containing therapy[26]. In this single-group, open-label study, 291 treatment-naïve patients infected with HCV genotype 1 were treated with sofosbuvir plus peg-interferon and ribavirin for 12 wk. The patients attained a high rate of SVR at 12 wk after completion of therapy (SVR12) (89%) and had a low rate of treatment discontinuation (2%) compared with historical controls. This study demonstrated the efficacy and safety of combining sofosbuvir with peginterferon and ribavirin; however, patients contraindicated for peginterferon or ribavirin were excluded.

Based on high rates of SVR in phase 2 studies, phase 3 ION studies (ION-1, ION-2 and ION-3 studies) were conducted to assess a fixed-dose combination of sofosbuvir and ledipasvir[27-30]. In the ION-1 trial, 865 treatment-naïve patients infected with HCV genotype 1 were randomly divided into four groups and received either 12 or 24 wk of sofosbuvir and ledipasvir with or without ribavirin. High SVR12 rates were attained in all groups (range: 97%-99%), and no patients in either 12-wk group discontinued therapy because of adverse events[28].

The ION-2 trial was conducted to evaluate the combination of sofosbuvir and ledipasvir with or without ribavirin in treatment-experienced patients. In this trial, 440 patients were divided into groups and treated with either 12 or 24 wk of sofosbuvir and ledipasvir with or without ribavirin. As in the ION-1 trial, high SVR12 rates were attained in all treatment groups (range: 94%-99%). No cases of treatment discontinuation owing to adverse events were reported[29].

The ION-3 trial was conducted to evaluate the feasibility of shorter duration therapy in previously untreated patients without cirrhosis. The noninferiority of an 8-wk regimen was demonstrated by the similar SVR12 rates in all groups (range: 93%-95%)[30]. The results from the ION-3 trial also indicated that an 8-wk regimen of sofosbuvir plus ledipasvir is not generally equal to 12 wk of treatment; however, international guidelines recommend that an HCV RNA threshold of 6 million IU/mL is maintained.

Among Asian countries, Mizokami *et al*[25] reported a phase 3 study conducted to evaluate Japanese patients. In this study, 166 treatment-naïve and 175 treatment-experienced patients received 12 wk of sofosbuvir and ledipasvir with or without ribavirin. High SVR12 rates (range: 96%-100%) were also attained in this study. This is noteworthy, as Japanese patients tend to be older, have more advanced fibrosis and are more frequently treated with previous therapy than patients in other countries. In the above studies, the inclusion of ribavirin in the treatment regimens produced no additional benefit. Furthermore, adverse events were more common in groups treated with ribavirin than in those without ribavirin.

The SOLAR-1 and SOLAR-2 studies showed the usefulness of sofosbuvir plus ledipasvir for decompensated cirrhosis[31,32]. In patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation, 86%-89% SVR12 rates were achieved[31]. In patients who had undergone liver transplantation, 96%-98%, 85%-88%, and 60%-75% SVR12 rates were achieved in patients without cirrhosis or with well-compensated cirrhosis, patients with

Table 2 Summary of phase 3 study for hepatitis C virus genotype 2-infected patients

Study name	Population	Treatment	Duration (wk)	*n*	LC (%)	SVR12 (%)		
						All	Non-LC	LC
FISSION	Naïve	SOF/RBV	12	70	-	97	-	-
POSITRON	IFN-ineligible/intolerant	SOF/RBV	12	109	15	93	92	94
VALENCE	Naïve	SOF/RBV	12	32	-	97	97	100
Japanese study	Naïve	SOF/RBV	12	90	9	98	97	100
FUSION	Experienced	SOF/RBV	12	36	28	86	96	60
			16	32	-	94	100	78
VALENCE	Experienced	SOF/RBV	12	41	-	90	91	88
Japanese study	Experienced	SOF/RBV	12	63	14	95	96	89

LC: Liver cirrhosis; SVR12: Sustained virologic response at 12 wk; Naïve: Treatment-naïve; Experienced: Treatment-experienced; SOF: Sofosbuvir; IFN: Interferon; RBV: Ribavirin.

moderate hepatic impairment, and patients with severe hepatic impairment, respectively[31]. All 6 patients with fibrosing cholestatic hepatitis achieved SVR12. Response rates in the 12- and 24-wk treatment groups were similar[31]. The use of sofosbuvir plus simeprevir for 12 and 8 wk in HCV genotype 1-infected patients without cirrhosis resulted in 83% and 97% SVR12 rates, respectively[33]. Likewise, the use of sofosbuvir plus simeprevir for 12 wk resulted in an 83% SVR12 rate in HCV genotype 1 - infected patients with cirrhosis[34].

HCV genotype 2-specific virologic response of sofosbuvir

The results from phase 3 clinical trials evaluating the use of treatments containing sofosbuvir against HCV genotype 2-infected patients are shown in Table 2. Three phase 3 trials have evaluated previously untreated patients (the FISSION, POSITRON and VALENCE studies)[23,29-31]. In the FISSION study, 12 wk of sofosbuvir plus ribavirin treatment and 24 wk of Peg-interferon α-2a (Peg-IFNα2a) plus ribavirin treatment produced comparable results in treatment-naïve patients. The SVR12 rate was 97% in a group of 70 patients who received sofosbuvir plus ribavirin and 78% in a group of 67 patients who received Peg-IFNα2a plus ribavirin. The noninferiority of the sofosbuvir plus ribavirin regimen relative to interferon-based therapy was shown. Furthermore, adverse events were less frequent with the sofosbuvir plus ribavirin regimen[26,35].

In the POSITRON study, 109 patients for whom treatment with Peg-IFN was not an option received 12 wk of sofosbuvir plus ribavirin, and 78% of these patients achieved SVR12[36]. These results were confirmed by the VALENCE study, in which 97% of 32 treatment-naïve patients achieved SVR12[37].

In addition, the FUSION study[36] and the other arm of the VALENCE study evaluated the use of a sofosbuvir plus ribavirin regimen in treatment-experienced patients. In the FUSION study, 103 patients received sofosbuvir plus ribavirin for 12 wk, and 98 patients received the treatment for 16 wk. The rates of SVR12 were 86% and 94% in the 12 and 16-wk groups, respectively[36].

Omata *et al*[38] reported the efficacy and safety of a 12-wk sofosbuvir plus ribavirin treatment in Japanese patients. The rates of SVR12 were 98% and 95% in treatment-naïve and previously treated patients, respectively. According to these trials, the use of sofosbuvir plus ribavirin has become a standard of care for the treatment of HCV genotype 2-infected patients.

HCV genotype 3-specific virologic response of sofosbuvir

HCV genotype 3 has become the most difficult genotype to cure in the era of interferon-free therapy. Although sofosbuvir is considered to have pangenotypic inhibitory activities, its treatment efficacy against HCV genotype 3 is lower than against the other genotypes. The results from phase 3 clinical trials evaluating treatments containing sofosbuvir to combat HCV genotype 3 are shown in Table 3.

In the FISSION study, SVR12 occurred in 56% of patients who received 12 wk of sofosbuvir plus ribavirin and in 63% of patients who received 24 wk of peginterferon plus ribavirin. These results were poor, as 97% of patients infected with HCV genotype 2 achieved SVR12 following treatment with sofosbuvir plus ribavirin in the same study[26,35].

The results of the POSITRON study were similar to those of the FISSION study. In the FISSION study, 61% patients infected with HCV genotype 3 achieved SVR12 compared to 93% of patients infected with HCV genotype 2. The rate of SVR12 in patients with cirrhosis was especially low in the HCV genotype 3 group (21%)[36].

Although the above results are somewhat disappointing, extending the duration of treatment might improve sofosbuvir's efficacy against HCV genotype 3. In the FUSION study, 16 wk of sofosbuvir plus ribavirin therapy resulted in higher SVR12 rates than 12 wk therapy (37% *vs* 63% in patients without cirrhosis; 19% *vs* 61% in patients with cirrhosis)[36].

In addition, the VALENCE study was conducted to assess the efficacy of 24 wk of sofosbuvir plus ribavirin treatment in 250 HCV genotype 3-infected patients[37]. The rates of SVR12 were 95% and 92% in treatment-naïve patients with and without cirrhosis, respectively, and 87% and 62% in previously treated patients with and without cirrhosis. A longer treatment duration

Table 3 Summary of phase 3 study for hepatitis C virus genotype 3-infected patients

Study name	Population	Treatment	Duration (wk)	*n*	LC (%)	SVR12 (%)		
						All	Non-LC	LC
FISSION	Naïve	SOF/RBV	12	183	-	56	-	-
POSITRON	IFN-ineligible/intolerant	SOF/RBV	12	98	15	61	68	21
VALENCE	Naïve	SOF/RBV	24	105	12	93	95	92
FUSION	Experienced	SOF/RBV	12	64	39	30	37	19
			16	63	-	62	63	61
VALENCE	Experienced	SOF/RBV	24	145	32	79	87	62

LC: Liver cirrhosis; SVR12: Sustained virologic response at 12 wk; Naïve: Treatment-naïve; Experienced: Treatment-experienced; SOF: Sofosbuvir; IFN: Interferon; RBV: Ribavirin.

Table 4 Summary of phase 3 study for hepatitis C virus-human immunodeficiency virus co-infected patients

Genotype	Study name	Population	Treatment	Duration (wk)	*n*	LC (%)	SVR12 (%)
1	PHOTON-1	Naïve	SOF/RBV	12	114	4.4	76
	PHOTON-2	Naïve	SOF/RBV	24	112	15	85
2	PHOTON-1	Naïve	SOF/RBV	12	26	-	88
		Experienced	SOF/RBV	24	24	-	92
	PHOTON-2	Naïve	SOF/RBV	12	19	5	89
		Experienced	SOF/RBV	24	6	33	83
3	PHOTON-1	Naïve	SOF/RBV	12	42	-	67
		Experienced	SOF/RBV	24	17	-	94
	PHOTON-2	Naïve	SOF/RBV	24	57	5	91
		Experienced	SOF/RBV	24	49	47	86
4	PHOTON-2	Naïve	SOF/RBV	24	31	26	84

LC: Liver cirrhosis; SVR12: Sustained virologic response at 12 wk; Naïve: Treatment-naïve; Experienced: Treatment-experienced; SOF: Sofosbuvir; RBV: Ribavirin.

was not associated with a higher frequency of adverse events or treatment discontinuation. However, further studies will be necessary to improve treatment efficacy in previously treated patients with cirrhosis.

Foster *et al*[23] reported a 93% SVR12 rate following 12 wk of treatment with peginterferon, sofosbuvir and ribavirin *vs* an 84% SVR12 rate following 24 wk of treatment with sofosbuvir plus ribavirin *vs* an 88% SVR12 rate following 12 wk of treatment with peginterferon, sofosbuvir and ribavirin in cirrhotic patients. Treatment with daclatasvir plus sofosbuvir for 12 wk led to a 96% SVR12 rate in HCV genotype 3-infected patients without cirrhosis[39].

Other HCV genotypes-specific virologic response of sofosbuvir

In the NEUTRINO study, 35 patients infected with HCV genotypes 4 through 6 were treated with sofosbuvir, ribavirin and peginterferon for 12 wk. The rates of SVR12 were 96% and 100% in patients infected with HCV genotypes 4 and 5-6, respectively[26]. A treatment regimen that contains sofosbuvir might therefore be efficient against these genotypes.

The use of a ribavirin- and interferon-free regimen of ledipasvir/sofosbuvir for 12 wk resulted in an SVR4 rate of 93% in genotype 4 and genotype 5 HCV-infected treatment-naïve and treatment-experienced patients with or without cirrhosis[40].

HIV co-infection

The PHOTON-1 and -2 studies were conducted to evaluate the use of sofosbuvir plus ribavirin therapy to combat HCV-human immunodeficiency virus (HIV) co-infection[41,42]. The results of these trials are summarized in Table 4.

In the PHOTON-1 study, in patients infected with HCV genotype 1, 12 wk of sofosbuvir plus ribavirin led to a 78% SVR12 rate. Extending treatment to 24 wk tended to result in higher rates of SVR (85%)[41].

The use of a longer treatment duration also appeared to be effective in treatment-naïve patients infected with HCV genotype 3. Similar to the results from the study against HCV genotype 3 infection alone, 12 wk of sofosbuvir plus ribavirin therapy attained low rates of SVR12 compared with other genotypes in the PHOTON-1 study (67%)[32]. Extending treatment from 12 to 24 wk improved the rate of SVR12 in the PHOTON-2 study (91%)[42]. Among patients infected with other HCV genotypes, high rates of SVR12 (83%-92%) were attained after 12 wk of sofosbuvir plus ribavirin treatment in treatment-naïve patients and 24 wk of the above treatment in previously treated patients[41,42].

The ALLY-2 study examined the use of daclatasvir plus sofosbuvir in patients co-infected with HIV and HCV genotype 1. The results showed that SVR rates were 96.4% following 12 wk of treatment and 75.6% following 8 wk of treatment in treatment-naïve patients.

The SVR12 rate was 97.7% in treatment-experienced patients following 12 wk of treatment with the above regimen[43].

The ION-4 study evaluated the use of ledipasvir plus sofosbuvir for 12 wk in HIV co-infected patients. The SVR12 rates were 96% in HCV genotype 1a-infected patients, 96% in HCV genotype 1b-infected patients, and 100% in HCV genotype 4-infected patients[44].

CONCLUSION

Sofosbuvir, a first-in-class NS5B inhibitor, has rapidly become the standard of care for the treatment of numerous HCV genotypes. However, its efficacy against HCV genotype 3, especially in patients with cirrhosis, has not been satisfactory. The optimal duration of treatment and use of novel combinations with other DAAs should be examined in the future.

Patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min per 1.73 m^2) and on hemodialysis are contraindicated for sofosbuvir-containing regimens. This limitation of sofosbuvir should be recognized. Nevertheless, sofosbuvir is an important drug that possesses high efficacy and safety. Sofosbuvir-containing therapy has become a standard of care for the majority of patients with HCV infections.

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