Sofosbuvir: A novel treatment option for chronic hepatitis C infection

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ABSTRACT

Hepatitis C currently infects more than 170 million people around the world, leading to significant morbidity and mortality. The current standard of care for HCV infection, including one of the two protease inhibitors, telaprevir or boceprevir, for 12-32 weeks, along with pegylated interferon alfa-2a (PEG-IFN-α) and ribavirin for up to 48 weeks, is unsatisfactory in many cases, either because of lack of efficacy or because of treatment-related adverse effects. There is an urgent need of new drugs with improved efficacy as well as a safety profile. Sofosbuvir, a recently approved nucleotide analog, is a highly potent inhibitor of the NS5B polymerase in the Hepatitis C virus (HCV), and has shown high efficacy in combination with several other drugs, with and without PEG-INF, against HCV. It offers many advantages due to its high potency, low side effects, oral administration, and high barrier to resistance. The efficacy and safety were demonstrated in many large and well-designed phase 2 and phase 3 clinical trials like NEUTRINO, PROTON, ELECTRON, ATOMIC, COSMOS, FUSION, FISSION, NUCLEAR, POSITRON, and the like. It is generally well-tolerated. Adverse events that occurred include: Headache, insomnia, fatigue, nausea, dizziness, pruritis, upper respiratory tract infections, rash, back pain, grade 1 anemia, and grade 4 lymphopenia; however, the exact safety profile can only be judged when this drug is actually used on a large scale.

Key words: Hepatitis C, NS5B polymerase, sofosbuvir, SVR

INTRODUCTION

Hepatitis C, caused by various genotypes of the Hepatitis C virus (HCV), currently infects more than 170 million people around the world. The infection may lead to chronic hepatitis, decompensated cirrhosis, and hepatocellular carcinoma, causing as many as 350,000 deaths per year.[1] The majority of the cases are caused by HCV genotypes 1 (70%) and 4, less frequently by types 2 and 3. The current standard of care for infection by HCV genotype-1 includes, one of the two protease inhibitors, telaprevir or boceprevir, for 12 - 32 weeks, along with pegylated interferon alfa-2a (PEG-IFN-α) and ribavirin for up to 48 weeks.[1] The treatment duration is guided by on-treatment response, allowing for shortening of the duration to 24 - 28 weeks in patients without cirrhosis, who show clearance of HCV RNA within the first eight weeks of therapy.[2] For genotypes 2 and 3, the recommended treatment is PEG-IFN-α and ribavirin for 24 weeks.[3]

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Sustained virological response (SVR), defined as undetectable HCV RNA in the serum for 24 weeks, after the end of treatment,

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is only seen in 60 - 80% of previously untreated patients and 55 - 60% of previously treated patients with HCV genotypes 2 and 3.[1,3,4] Higher SVR is seen in genotype 1 infections with triple therapy, in the range of 69 - 88% in previously untreated and 59 - 68% in previously treated patients.[5] SVR is associated with improved outcomes in the form of reduction in the rate of hepatocellular carcinoma (HCC) and liver decompensation, and improved survival; patients who achieve SVR are considered to be cured.[6]

In addition to the patient population that is not cured by the available regimens, is the burden of numerous patients who go untreated due to contraindications (advanced hepatic disease, autoimmune disease, and psychiatric illness) or refusal to receive interferons, as well as poor compliance or discontinuation of therapy due to adverse effects (fatigue, headache, fever, cytopenia, autoimmune disorders, insomnia, and depression). Other downsides of interferons include their need to be injected and the long duration of treatment. Although regimens containing protease inhibitors have resulted in higher SVR and shorter duration of treatment, their limitations include a low genetic barrier to resistance, more side effects, complex medication regimens, and a potential for drug interactions.[2,5,6] In patients who do not achieve SVR with the current treatment options as well as those that go untreated, newer options are required. Researchers are now evaluating the combination of two or more antiviral agents, with separate targets for possible interferon-free regimens with higher SVR and shorter duration of treatment.[1,5,7]

WHAT IS SOFOSBUVIR?

Sofosbuvir is a new drug candidate for hepatitis C treatment, with the chemical name L-Alanine, N-[[P(S),2'R]-2'-deoxy-2'-fluoro-2'-methyl-P-phenyl-5'-uridylyl]-, 1-methylethyl ester and a molecular formula of C22H29FN3O9P.[8] Previously known as PS-7977 or GS-7977, it has shown promising results in numerous *in vitro* studies against all the genotypes of HCV. It is a nucleotide analog that is a highly potent inhibitor of the NS5B polymerase in HCV. This drug has shown high efficacy in combination with several other drugs with and without PEG-INF, against HCV. Sofosbuvir is of special interest among the directly acting antiviral drugs under development, due to its high potency, low side effects, oral administration, and high barrier to resistance.

MECHANISM OF ACTION

Hepatitis C virus is a single-stranded RNA virus, and its open-reading frame encodes ten structural proteins (viral capsid and envelope) and non-structural proteins (required for viral replication). NS5B is one of the non-structural proteins essential for viral RNA replication, and has been found to be a valuable target for directly acting antiviral agents (DAAs).[9] The uridine nucleotide analog sofosbuvir is a phosphoramidate prodrug that has to be triphosphorylated within the cells to produce its action. The required enzymes for its activation are present in the human hepatic cells, therefore, it is converted to its active metabolite during the first-pass metabolism, directly at the desired site of action: The liver.[5] The metabolic pathway for activation of the prodrug[5,10] is shown in Figure 1. This analog then mimics the physiological nucleotide and competitively blocks the NS5B polymerase, thus inhibiting the HCV-RNA synthesis by RNA chain termination.[4,7] The catalytic site of the enzyme is also highly conserved across all the HCV genotypes, accounting for pan-genotypic efficacy of sofosbuvir.[5]

PHARMACOKINETICS OF SOFOSBUVIR

Several studies on the pharmacokinetics of sofosbuvir have been carried out[6,11,12] and some are ongoing at present[13-15] – alone and in combination with other drugs. Sofosbuvir has a beneficial pharmacokinetic profile, being effective orally as a single daily dose; this is likely to improve the compliance compared to protease inhibitors (with multiple oral daily doses), and PEG-IFN (parenteral administration). Absorption and elimination were observed after single and multiple doses of sofosbuvir, the results are shown in Table 1. The metabolic activation of the prodrug takes place by the enzymes present in the human liver [Figure 1]. A systemic exposure of >90% is due to the metabolite GS-331007 (previously PSI-6206), which also has a longer t_{max} and elimination $t_{1/2}$ than sofosbuvir.[5,11-16]

The effect of hepatic impairment was studied in a seven-day treatment with sofosbuvir in 17 patients with moderate-to-severe HCV-related hepatic impairment compared to eight non-cirrhotic patients infected with HCV. There was

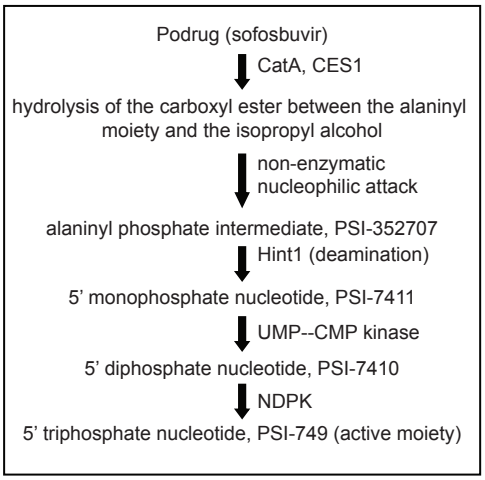

Figure 1: Activation of sofosbuvir in liver. CatA -human cathepsin A; CES1- carboxylesterase 1; Hint1 - histidine triad nucleotide-binding protein 1; NDPK – nucleoside diphosphate kinase; UMP–CMP kinase-uridine monophosphate–cytidine monophosphate kinas

Table 1: Pharmacokinetics of sofosbuvir[6,11]

Metabolite	T_{max} (hours)	Elimination $T_{1/2}$ (hours)	Substrate for P-glycoprotein
Sofosbuvir (prodrug)	1 (0.5-3)	0.48-0.75	Yes
GS-331007	4 (1.5-8)	(7.27-11.8)	No
GS-566500	-	-	Yes

Values in median (range)

no significant difference in the half-life with or without hepatic impairment. The C_{max} was 80% higher, and the AUC was 130% higher in subjects with hepatic impairment, while the viral decline was less pronounced. The safety profile was good in all the patients, thus suggesting that no dosage or interval modification was required in patients with moderate-to-severe hepatic impairment.[6]

The effect of renal impairment on the pharmacokinetics of sofosbuvir has also been studied with a single 400 mg dose, in patients with varying degrees of renal impairment. The AUC of an inactive nucleotide metabolite, PSI-6206, is increased by 56% in mild, 90% in moderate, and 456% in severe renal impairment subjects, compared to normal subjects. Dosage or interval modifications are thus suggested in patients with moderate-to-severe renal impairment. Furthermore, 15% of sofosbuvir and 53% of PSI-6206 have been extracted by hemodialysis in patients with end-stage renal disease; dosage modifications will be recommended in this group of patients.[11]

EFFICACY

The efficacy and safety of sofosbuvir in patients with different HCV genotypes and with various combinations of drugs have been tested in numerous clinical trials. A dose of 400 mg of sofosbuvir has been found to be most effective, with treatment durations ranging from 12 to 24 weeks, in various combinations of PEG-IFN and ribavirin in phase 2 clinical trials [Table 2]. The NEUTRINO study found SVR to be 90% (95% CI, 87 to 93) 12 weeks after therapy with sofosbuvir + PEG-INF + ribavirin; this was found to be superior to the adjusted historical response rate of 60% ($P < 0.001$).[1] Similar positive results have been found in numerous phase 3 clinical trials [Table 3]. Furthermore, recent phase 1 and 2 studies of sofosbuvir in combination with other DAAs have also shown promising results [Table 2].

ONGOING TRIALS

Numerous studies are either recruiting or active at present, evaluating sofosbuvir in different populations of patients and with different drug combinations for varying durations. Sofosbuvir plus ribavirin all-oral combinations are being assessed in specific populations such as those having HCV genotype 4, in patients with renal insufficiency, concomitant HIV, hepatocellular carcinoma pre-transplantation, chronic HCV with cirrhosis and portal hypertension, or recurrent chronic HCV post liver transplant. The combination of sofosbuvir, ribavirin, plus PEG-INF is being evaluated in some ongoing trials including the FISSION and NEUTRINO trials, as well as in patients with aggressive post-transplant hepatitis. Several studies are underway evaluating the fixed dose combination of sofosbuvir 400 mg + ledipasvir (NS5A inhibitor, GS-5885) 90 mg, in the different HCV genotypes. Other drugs being tested in combination with sofosbuvir in ongoing trials include: GS-9669 (NS5B non-nucleoside thumb site II inhibitor) and GS-5816 (second-generation NS5A inhibitor).[5-7,12-15,23]

RESISTANCE

DAAs, including NS3/4 A protease inhibitors and NS5A inhibitors, have shown beneficial results in the treatment of HCV; however, this is at the cost of rapidly emerging resistance, resulting in either a virological breakthrough during the treatment or a relapse thereafter. The high genetic barrier to resistance to sofosbuvir distinguishes it from other members in this group.[1,4-6]

Cross-resistance studies have been conducted using panels of replicons with mutations in the NS3/4A protease, NS5A, and NS5B, which remained susceptible to sofosbuvir (except for HCV type 1b S282T), thus indicating that sofosbuvir can be combined with other directly acting antiviral agents. It has been suggested that additional mutations with amino acids change in both the finger and palm domains (T179A, M289L, and I293L) and are required to compensate for poor HCV fitness, resulting from S282T mutation, in order to confer resistance to sofosbuvir. The S282T mutation has so far only been detected in one patient, with HCV type 2b; a relapse has been seen in this patient after sofosbuvir monotherapy. Genotype or subtype-specific resistance has not been seen with sofosbuvir.[6,9]

In the clinical studies, although relapse leading to treatment failure was seen in a few patients, no virological resistance was detected in these patients receiving sofosbuvir 400 mg monotherapy or in combination with either ribavirin, PEG-INF or both.[16] One patient in the FISSION trial had a virological breakthrough, but this was most probably the result of non-compliance, as the levels of sofosbuvir were not detectable in the patient.[24] The presence of a high barrier of resistance to sofosbuvir is a result of the highly conserved nature of the NS5B polymerase; variants in the active site of this enzyme result in the detrimental condition of the virus.[4,7]

Table 2: Phase 1 and 2 clinical studies involving sofosbuvir

Authors	Study	Patients	Comparator	Results (SVR)	Adverse events
Lawitz *et al.* Nuclear study[17]	Phase 1, proof-of-concept study of purine (PSI-938)/ pyrimidine (sofosbuvir) combination	40 treatment naïve patients with HCV type 1	a) PSI-938 300 mg q.d. for 14 days b) PSI-938 300 mg q.d. for 7 days then combined with sofosbuvir 400 mg q.d. for 7 days c) Sofosbuvir 400 mg q.d. for 7 days then combined with PSI-938 400 mg q.d. for 7 days d) PSI-938+sofosbuvir for 14 days Followed by full course of Peg-INF+Ribavirin on day 15	Number of subjects with undetectable HCV RNA- a) 50% b) 100% c) 88% d) 88%	Headache, fatigue, non-cardiac chest pain, dizziness-all mild
Rodriguez-Torres *et al.*[16]	Phase 2, double-blind, randomized, placebo-controlled, dose-ranging study	64 Treatment naïve patients with HCV Type 1	Peg-INF+Ribavirin+either: a) Sofosbuvir 100 mg b) Sofosbuvir 200 mg c) Sofosbuvir 400 mg d) Placebo -for 28 days, followed by Peg-INF+Ribavirin for 44 weeks	SVR24- a) 56% b) 83% c) 80% d) 43%	Fatigue and nausea
Levin (Lalezari *et al.*) Proton study[18]	Phase 2, double-blind, randomized, placebo-controlled, dose-ranging study	121 patients with HCV type 1 (2:2:1), 25 patients with HCV type 2 or 3: All treatment naïve patients	Response-guided duration (12 or 36 weeks) of Peg-IFN and Ribavirin+either a) Sofosbuvir 200 mg, or b) Sofosbuvir 400 mg, or c) Placebo for initial 12 weeks d) Peg-IFN+ribavirin+sofosbuvir 400 mg for 12 weeks	SVR12 - HCV type 1 - a) 90% b) 91% c) < 50% HCV type 2 and 3 d) 96%	Insomnia more in (c); Others: Nausea, chills, fatigue, depression, headache in all groups
Gane *et al.* Electronstudy[19]	Phase 2, randomized clinical study	145 Previously treated and untreated patients with HCV type 1, 2, 3	11 arms in the study HCV type 2/3 given either a) Sofosbuvir+Ribavirin +/- PEG-INF for 12 weeks, or triple therapy for 8 weeks, or b) Sofosbuvir monotherapy for 12 weeks c) Sofosbuvir+either low dose (800 mg) or short duration (8 weeks) of ribavirin HCV type 1-sofosbuvir+ribavirin for 12 weeks in d) treatment naïve or e) previous null-responders	SVR 24 - HCV type 2/3- a) 100% b) 60% c) < 64% SVR 24 HCV Type 1 - d) 84% e) 10%	headache, fatigue, insomnia, nausea, rash, and anemia
Kowdley *et al.* Atomic study[2]	Phase 2, open-label, randomized trial	Non-cirrhotic, treatment naïve patients with HCV type 1 (316 patients), 4 (11 patients), 6 (4 patients)	Sofosbuvir 400 mg+PegINF+Ribavirin for a) 12 weeks or b) 24 weeks or c) 12 weeks followed by either sofosbuvir alone or sofosbuvir+ribavirin for 12 weeks	SVR24 - HCV type 1 - a) 89% (95% CI, 77-96) b) 89% (82-94) c) 87% (81-92) HCV type 4-82%; HCV type 6-100%	Anemia and neutropenia associated with PEG-INF and Ribavirin Discontinued due to AE- a - 6%, b - 14%, c - 2%
Osinusi *et al.*[20]	Phase 2 - Single-center, open-label study - Part 1	10 treatment-naive patients with HCV genotype 1, unfavorable treatment characteristics-early to moderate liver fibrosis	400 mg/d of sofosbuvir and weight-based ribavirin for 24 weeks	SVR24-90% (95% CI, 55-100%)	headache, anemia, fatigue, and nausea; neutropenia, hypophosphatemia, cholelithiasis, and pancreatitis
Osinusi *et al.*[20]	Phase 2 - Single-center, randomized, open-label study -Part 2	50 treatment-naive patients with HCV genotype 1, unfavorable treatment characteristics - all stages of liver fibrosis	400 mg of sofosbuvir with either a) weight-based or b) low-dose 600 mg/d of ribavirin for 24 weeks	SVR24- a) 68% (95% CI, 46-85%) b) 48% (95% CI, 28-69%) (*P*=0.20)	

Contd...

Table 2: Contd...

Authors	Study	Patients	Comparator	Results (SVR)	Adverse events
Lawitz *et al.* Cosmos trial[21]	Phase 2a, Open-label study with NS3/4A protease inhibitor Simeprevir+ sofosbuvir	80 Prior null-responders with HCV type 1 40% - absent to mild liver fibrosis, 60% - advanced liver fibrosis or cirrhosis	150 mg OD simeprevir plus 400 mg OD sofosbuvir, either a) dual therapy for 12 weeks OR b) plus 1000-1200 mg/day weight-adjusted ribavirin, for 12 weeks c) dual therapy for 24 weeks d) plus 1000-1200 mg/day weight-adjusted ribavirin, for 24 weeks	Interim analysis SVR8 a) 93% b) 96%	Mild to moderate, 1 discontinuation Anemia less in (a) than (b)
Sulkowski *et al.*[22]	Open-label phase 2a trial with daclatasvir±ribavirin	170 treatment naïve patients with HCV type 1, 2, 3	8 arms, receiving sofosbuvir 400 mg+daclatasvir 60 mg either a) without ribavirin for 24 weeks b) with ribavirin for 24 weeks c) without ribavirin for 12 weeks d) with ribavirin for 12 weeks	SVR 24 in HCV type 1-98% HCV type 2 or 3-93%	fatigue, headache, nausea, alopecia, arthralgia, constipation Anemia clearly associated with ribavirin

SVR=Sustained virological response, HCV=Hepatitis C virus, q.d. – four times a day

Table 3: Phase 3 clinical trials involving sofosbuvir

Authors	Study	Patients	Comparator	Results (SVR)	Adverse events
Lawitz *et al.* Neutrino study[1]	Single group open-label study: Phase 3	327 patients with HCV Type 1 and 4 (98%), 5, 6; previously untreated	Sofosbuvir+PEG-INF-2a+Ribavirin for 12 weeks	SVR12-90% (95% CI, 87 to 93) Cirrhosis - 81%	Fatigue, headache, nausea, insomnia, neutropenia was less with sofosbuvir than PEG-INF; similar rates of dizziness and anemia with both
Lawitz *et al.* Fission study[1]	Randomized clinical trial; non-inferiority study: Phase 3	499 patients with HCV type 2 and 3; previously untreated	sofosbuvir+ ribavirin for 12 weeks OR PEG INF-2a+ribavirin for 24 weeks	SVR12-67% in both groups at 12 weeks Type 2-97% Type 3-56% No cirrhosis: 72% Cirrhosis: 47%	
Jacobson *et al.* Positron study[3]	Phase 3, Randomized, placebo-controlled trial	272 patients with HCV type 2 or 3, for whom treatment with PEG-INF was not an option	a) Sofosbuvir+ Ribavirin (207 patients) OR b) Placebo+Ribavirin for 12 weeks	SVR12 - a) 78% (95%CI, 72 to 83) b) 0% with placebo (P<0.001) - lower in type 3 and cirrhosis	headache, fatigue, nausea, and insomnia
Jacobson *et al.* Fusion study[3]	Phase 3, Randomized clinical trial	Patients with HCV type 2 or 3, with no response to previous PEG-INF	a) sofosbuvir and ribavirin for 12 weeks (103 patients) or b) 16 weeks (98)	SVR12 - a) 50% b) 73% Difference 23%age points, 95% CI, - 35 to 11 (P<0.001) - lower in type 3 and cirrhosis	headache, fatigue, nausea, and insomnia

SVR=Sustained virological response, HCV=Hepatitis C virus, PEG-INF=Pegylated interferon

ADVERSE EFFECT PROFILE OF SOFOSFUVIR

Sofosbuvir has shown a good safety profile in clinical trials; a small decrease in the Hb levels (0.54 mg/dl) and reduction in the cumulative events in comparison to interferon-containing regimens is seen. Common adverse events observed include: Headache, insomnia, fatigue, nausea, dizziness, pruritis, upper respiratory tract infections, rash, back pain, grade 1 anemia, and grade 4 lymphopenia [Tables 2 and 3]. No neutropenia, thrombocytopenia, or any serious adverse events are associated with sofosbuvir treatment. In the monotherapy treatment groups, nausea and fatigue seemed to be the only adverse events possibly correlated to sofosbuvir. An overall improved tolerability was seen with sofosbuvir compared to the interferon-based regimens.[5,6,25]

DRUG INTERACTIONS OF SOFOSBUVIR

Many patients with HCV have concomitant illnesses such as HIV requiring anti-retroviral therapy, or hepatocellular carcinoma/ decompensated liver disease requiring liver transplants along with immunosuppressant medication. Thus, it is very important to study the possible drug interactions that may occur in these patients, who also require treatment of HCV. Studies have shown no clinically significant interactions between sofosbuvir and the following drugs: Cyclosporine, tacrolimus, methadone, efavirenz, rilpivirine, darunavir/ritonavir, raltegravir, and tenofovir. No dose adjustments are required in patients receiving these drugs along with sofosbuvir. As sofosbuvir is being tried for all-oral regimens combined with other directly acting antiviral agents, interactions with these drugs have

also been studied. No clinically significant interactions have been found between sofosbuvir and daclatasvir, ledipasvir, or GS-9669.[5,11,24] A 54-year-old liver transplant recipient with HCV type 1b and severe recurrent cholestatic hepatitis was given daclatasvir (HCV NS5A inhibitor) plus sofosbuvir for 24 weeks; SVR at 36 was achieved, and the level and dose of tacrolimus remained stable in this patient.[26]

CURRENT STATUS

The US FDA has recently (6 December, 2013) approved sofosbuvir under the brand name Sovaldi for the treatment chronic HCV infection under a breakthrough therapy designation, because it has shown a substantial improvement over the other available therapies. The most interesting feature of this approval lies in the fact that this drug can be administered without the need of interferon therapy. On the basis of the type of HCV infection, the treatment regimen may include sofosbuvir and ribavirin/sofosbuvir, ribavirin, and Peg-interferon-alfa. Earlier it was under the FDA's priority review program (an expedited review of drugs useful for serious conditions, which, after their approval, would provide significant improvement in safety or effectiveness). Positive results from major clinical trials, plus a demonstration of efficacy in patients who cannot tolerate interferon-based regimens and in patients with liver cancer undergoing liver transplantation, make this drug a valuable and very useful therapy for these patient populations.[27]

CONCLUSION

From the above discussion, it seems that sofosbuvir is a promising therapy for chronic HCV infection, as it offers several advantages over the existing therapies, particularly in dealing with patients with decompensated liver disease and patients who cannot tolerate interferon-containing therapies. On account of its excellent performance in clinical trials, this drug has got FDA approval on 6 December, 2013, under the breakthrough therapy designation. This drug is effective against all HCV genotypes, has a better safety profile, and low risk of development of resistance; however, careful clinical use and monitoring is still essential, to gather more data on this drug. Large post-marketing studies, including pharmacoepidemiological and pharmacovigilance studies, can solve many unanswered questions for the future of this novel drug. As of now, sofosbuvir is among the most promising agents available for the treatment of chronic HCV infection.

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