International Journal of Advanced Research and Development
ISSN: 2455-4030
Impact Factor: RJIF 5.24
www.advancedjournal.com
Volume 3; Issue 2; March 2018; Page No. 1025-1027

Sofosbuvir for chronic hepatitis C: A review

Priya G Shete[1*], Neha G Shete[2], Rupali H Tiple[3]
[1, 2] Department of Pharmaceutics, Agnihotri College of Pharmacy Wardha, Maharashtra, India
[3] Shree Babasaheb Gharfalkar College of Pharmacy, Pulgaon, Wardha, Maharashtra, India

Abstract
Hepatitis C virus (HCV) infection affects as many as 185 million people worldwide. Since the emergence of new direct-acting agents (DAAs), interferon-free therapy has become the cornerstone of treatment. Major changes have emerged during the last few years in the therapy of patients with chronic hepatitis C (CHC). Several direct acting antiviral agents have been developed showing potent activity against hepatitis C virus and incrementally improving the rates of sustained virological response (SVR), even in difficult-to-treat CHC patients. Sofosbuvir, a new nucleotide analog, HCV NS5B polymerase inhibitor, represents the first key step towards the new era in the management of CHC, since it is the first approved DAA with excellent tolerability and favorable pharmacokinetic profile, limited potential for drug interactions, potent antiviral activity and high genetic barrier against all HCV genotypes. Sofosbuvir has recently become commercially available in combination with ribavirin, with or without pegylated interferon, achieving high SVR rates after 12-24 weeks of therapy. Finally, since interferon-free regimens are close to becoming the new standard of care in CHC patients, sofosbuvir has an ideal profile to be the cornerstone antiviral agent, especially in difficult-to-treat CHC patients, given in combination with other new DAAs. This review summarizes the main updated issues related to the efficacy and safety of sofosbuvir-containing regimens in CHC patients.

Keywords: sofosbuvir, hepatitis C, direct acting antiviral agents, efficacy, safety

Introduction
Hepatitis C virus is associated with a substantial disease burden in the western world. It is the leading cause of chronic hepatitis, cirrhosis, and liver cancer, and is a primary indication for liver transplantation [1]. As many as 185 million persons worldwide, including 3.4 to 4.4 million in the United States, are chronically infected with HCV; 3 to 4 million individuals are estimated to be newly infected each year [2, 3]. Acute infection develops within 2 to 26 weeks after HCV exposure [4, 5]. Some of these acutely infected patients may spontaneously clear HCV, but the majority will progress to chronic infection [6]. Approximately 25% of chronically infected persons will develop cirrhosis. Progression to cirrhosis was thought to occur gradu tually death [7]. Upwards of 350,000 people worldwide die from HCV-related complications each year non-structural proteins. The structural proteins include capsid protein C and the envelope glycoproteins E1 and E2. The non-structural proteins include porin p7, autoprotease and assembly factor NS2, serine protease and RNA helicase NS3, NS3 protease co-factor NS4A, the organizer of replication complex and membranous web NS4B, the regulator of replication and viral assembly NS5A, and RNA-dependent RNA polymerase NS5B. The resulting HCV polypeptide is cleaved by cellular proteases and viral NS2/3 and NS3/4A proteases to release the ten HCV proteins [8]. The replication complex is formed next. NS5A plays an important role in the formation of this replication complex [9, 10]. Two NS3-4A serine protease inhibitors, boceprevir and telaprevir, were the first generation DAAs approved for clinical use in genotype 1 CHC patients in mid 2011. With the triple combination of pegIFN, RBV and boceprevir or telaprevir, the probability of SVR increased by 30% in naïve patients, by 50-60% in relapsers and by 25% in null responders [11]. Pregnancy should be avoided in both female patients and female partners of male patients who receive any current sofosbuvir containing regimen and for at least 6 months following cessation of therapy [12]. No dose adjustment of sofosbuvir is recommended for patients with moderate and severe hepatic dysfunction [13].

Mechanism of action
Sofosbuvir is a newer antiviral drug which upon its conversion in the liver to its active form serves as a nucleotide polymerase inhibitor. The activated drug (2‟-deoxy-2‟-α-fluoro-β-C-methyluridine-5‟-triphosphate), actsas a defective substrate for the RNA polymerase. Once this analogue is bound to the RNA polymerases, further synthesis of viral RNAs are inhibited which in turn leads to the terminationof viral replication [14, 15, 16, 17].

Pharmacodymamics-pharmacokinetics of sofosbuvir
Sofosbuvir, originally termed as PSI-7977, is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B RNA-dependent RNA polymerase (RdRp) acting as a chain terminator. Studies in replicon cells containing different HCV genotypes showed that sofosbuvir is active against all HCV genotypes without any antagonistic effect in co-administration of interferon or RBV [18]. Sofosbuvir results in

rapid reduction of viral load. Although HCV variants with the S282T mutation causing reduced susceptibility against sofosbuvir have been identified in vitro clinical studies demonstrated that sofosbuvir has a high resistance barrier, since no S282T mutation was detected in patients who relapsed after receiving sofosbuvir in combination with RBV with or without pegIFN or a second DAA [18]. This mutation was detected in one HCV genotype 2b patient at week 4 after treatment with sofosbuvir monotherapy in the ELECTRON phase II study indicatingthat sofosbuvir should not be used as monotherapy. Sofosbuvir has a very favour able pharmacokinetic profile.

Following oral administration, peak plasma concentrations of sofosbuvir and its major circulating metabolite GS-331007 are achieved after 0.5-2 and 2-4 h respectively [19], without being affected by food administration. It is approximately 61-65% bound to human plasma proteins and is eliminated genotype 1, 4, 5 or 6, who received sofosbuvir plus pegIFNa-2a (180 μg per week) and weight-based RBV (total daily dose of 1000 or 1200 mg for those with body weight ≤75 or >75 kg, respectively) for 12 weeks. Of the 327 patients, 17% had cirrhosis. Genotype 1 patients, who represented 89% of the patient population, achieved high SVR rate of 90% (1a: 92%; 1b: 82%). SVR rates were lower in cirrhotics than non-cirrhotics (80% vs. 93%), while they were not affected by race, gender, body mass index and baseline viral load. Only 1.5% of patients discontinued treatment due to adverse events. No virological breakthroughs occurred during treatment and no resistance-associated variants were detected among patients who relapsed after the end of treatment [20].

Treatment of HCV

The primary outcome in HCV clinical trials is sustained virologic response 12 weeks after the end of treatment (SVR12), defined as undetectable HCV RNA serum levels. Analyses of HCV infection and advanced hepatic fibrosis and in patients with HCV-HIV coinfection, including both liver-related and non-liver-related mortality [21-22]. The combination of peginterferon and ribavirin was considered the standard of care for patients with HCV for many years [23]. The introduction of direct-acting agents in 2011, specifically first-generation NS3/4A protease inhibitors, led to interferon-sparing combinations resulting in a shorter duration of therapy with a higher rate of virologic cure [24]. As more classes of DAAs were introduced, agents from two or more classes could be combined to eliminate the need for peginterferon, which was previously needed to reduce the emergence of resistance to protease inhibitors [25]. Disease association is largely similar across all HCV genotypes, but treatment response varies [26]. Genotype 3, for example, has improved rates of SVR with peginterferon and ribavirin compared to genotypes 1 or 4. However, it also had diminished clinical benefits in response to the first-generation HCV protease inhibitors telaprevir and boceprevir. The results of clinical trials have confirmed that the non-CC IL28B genotype, which is associated with poor response to peginterferon-containing regimens, is not associated with poor response to interferon-free treatments [27, 28].

Safety profile of Sofosbuvir

Sofosbuvir has an excellent tolerability and safety profile. This has been assessed in several clinical trials including more than 3000 CHC patients, with the majority of clinical adverse events being of grade 1 severity. Most severe adverse events have been observed in sofosbuvir combinations with RBV and/or pegIFN. In the clinical trials of sofosbuvir, the proportion of CHC patients who discontinued treatment due to adverse events was 4% in placebo groups, 1% in sofosbuvir plus RBV groups and 2% in sofosbuvir plus pegIFN and RBV groups [29]. Its excellent safety profile makes sofosbuvir an optimal choice for patients with decompensated cirrhosis and liver transplant recipients as well as for patients who cannot tolerate interferon and/or RBV.

Discussion

The approval of sofosbuvir represents the first key step towards the new era in the management of CHC patients, since it is the first approved DAA with potent activity and high genetic barrier against all HCV genotypes [30]. In addition, its safety profile is excellent, even when it is given in patients with very advanced liver disease and high risk of complications (e.g. cirrhotics with portal hypertension, liver transplant impairment, liver transplant recipients, co-infection with human immunodeficiency virus and other co-morbidities. In particular, 8-12 week courses with the combination of sofosbuvir with a potent NS5A inhibitor (e.g. ledipasvir or daclatasvir) or NS3 protease inhibitor (e.g. simeprevir) have been shown to achieve SVR in almost all genotype 1 patients without safety and tolerability concerns. However, despite all such amazing scientific progress and the potential to cure HCV in all CHC patients regardless of the liver disease severity, the high cost of the new DAAs including sofosbuvir is raising discussions and public health debates about their optimal and most cost-effective use which may differ among different countries.

References

1. Lavanchy D. The global burden of hepatitis C. Liver Int. 2009; 29(Suppl 1):74-81.
2. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol, 2007; 13:2436-2441.
3. Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. Best Pract Res Clin Gastroenterol 2012; 26:401-412.
4. Terrault N. Liver transplantation in the setting of chronic HCV. Best Pract Res Clin Gastroenterol. 2012; 26:531-548.
5. Alexopoulou A, Papatheodoridis GV. Current progress in the treatment of chronic hepatitis C. World J Gastroenterol, 2012; 18:6060-6069.
6. Papatheodoridis GV, Cholongitas E. Chronic hepatitis C and no response to antiviral therapy: potential current and future therapeutic options. J Viral Hepat. 2004; 11:287-296.
7. Cholongitas E, Papatheodoridis GV. Review article: novel therapeutic options for chronic hepatitis C. Aliment Pharmacol Ther. 2008; 27:866-884.

8. Lawitz E, Mangia A, Wyles D, *et al*. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013; 368:1878-1887.16. Gane EJ, Stedman C
9. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. N Engl J Med. 2013; 368(20):1907-1917.
10. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. Nature 465(7294):96-100.
11. Alexopoulou A, Papatheodoridis GV. Current progress in the treatment of chronic hepatitis C. World J Gastroenterol. 2012; 18:6060-6069.
12. Smith db, Bukh j, Kuiken C, Muerhoff AS, Rice CM, *et al*. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology. 2014; 59(1):318-327.
13. Kirby B, Gordi T, Symonds W, Kearney B, Mathias A. Population pharmacokinetics of sofosbuvir and its major metabolite (GS-331007) in healthy and HCV infected adult subjects. Hepatology. 2013; 58(Suppl 4):746A.
14. Sofosbuvir: Australian Prescriber. [homepage on the Internet]. c2015 [cited 2015 Aug 6]. Availablefrom:http://www.australianprescriber.com/magazine/37/5/172/79/newdrugs/1066/sofosbuvir-for-hepatitis-C.
15. Sofosbuvir: Canada‟s source for HIV and hepatitis C information. [homepage on the Internet]. c2015 [cited 2015 Aug 6]. Available from: http://www.catie.ca/en/fact-sheets/hepatitis/sofosbuvir-sovaldi.
16. Sofosbuvir: DrugBank. [homepage on the Internet]. c2015 [cited 2015 Aug 6]. Available from: http://www.drugbank.ca/drugs/DB08934.
17. Sofosbuvir: Pubchem. [homepage on the Internet]. c2015 [cited 2015 Aug 6]. Available from: http://pubchem.ncbi.nlm.nih.gov/compound/sofosbuvir#section=Top.
18. Keating GM, Vaidya A. Sofosbuvir: first global approval. Drugs, 2014; 74:273-282.
19. Kirby B, Gordi T, Symonds W, Kearney B, Mathias A. Population pharmacokinetics of sofosbuvir and its major metabolite (GS-331007) in healthy and HCV infected adult subjects. Hepatology. 2013; 58(Suppl 4):746A.
20. Lawitz E, Mangia A, Wyles D, *et al*. Sofosbuvir for previously untreated chronic hepatitis C infection. NEngl J Med. 2013; 368:1878-1887.
21. vander Merr AJ, Veldt BJ, Wedemeyer H, Dufour JE *et al*. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012; 308(24):2584-2593.
22. Berenguer J, Alvarez-Pellicer J, Martín PM, López-Aldeguer J, Von-Wichmann MA, *et al*. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology. 2009; 50(2):407-413.
23. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. N Engl J Med. 2006; 355(23):2444-2451.
24. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. Lancet. 2015; 385(9973):1124-1135.
25. FakhriRavari A, Malakouti M, Brady R. Interferon-Free Treatments for Chronic Hepatitis C Genotype 1 Infection. J Clin Transl Hepatol. 2016; 4(2):97-112.
26. Scheel TK, Rice CM. Understanding the hepatitis C virus life cycle paves the way for highly effective therapies. Nat Med. 2013; 19:837-849.
27. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, *et al*. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009; 461(7262):399-401.
28. Kowdley KV. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014; 370:1879-1888.
29. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, *et al*. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989; 244(4902):359-362.
30. Sovaldi R. [package insert]. Gilead Sciences, Inc, Foster City, California, USA, 2015.