wjpmr, 2018,4(12), 143-148

SJIF Impact Factor: 4.639

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

SOFOSBUVIR, THE NUCLEOTIDE ANALOGUE AGAINST HEPATITIS C VIRUS – A REVIEW

Soumya S P[*1], Sinchu Yesudanam[1], Anusree S[1], Dr. William Arputha Sundar A S[2] and Sam Jeeva Kumar E[3]

[1]Assistant Professor, Sreekrishna College of Pharmacy and Research Center, Trivandrum.
[2]Principal, Sreekrishna College of Pharmacy and Research Center, Trivandrum.
[3]Head, Department of Pharmacology, Sreekrishna College of Pharmacy and Research Center, Trivandrum.

***Corresponding Author: Soumya S. P.**

Assistant Professor, Sreekrishna College of Pharmacy and Research Center, Trivandrum.

Article Received on 24/09/2018 **Article Revised on 15/10/2018** **Article Accepted on 05/11/2018**

ABSTRACT

Infectious liver disease caused by the hepatitis C virus. There is no vaccine and it commonly becomes chronic. Traditional treatment is limited by frequent adverse effects and low efficacy. The current therapy for HCV infection, includes one of the two protease inhibitors, telaprevir or boceprevir, for 12-32 weeks with pegylated interferone interferon alfa-2a (PEG-IFN-α) and ribavirin for 48 weeks. Sofosbuvir, a recently approved nucleotide analog, is a highly potent inhibitor of the NS5B polymerase in the Hepatitis C virus (HCV), and has shown 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.

KEYWORDS: Telaprevir, boceprevir, pegylated, Sofosbuvir.

INTRODUCTION

Hepatitis means inflammation of the liver. The Ancient Greek word "*hepa"* refers to the liver, and "itis" means inflammation. Some people have no symptoms whereas others develop yellow discoloration of the skin and whites of the eye, poor appetite, vomiting, tiredness, abdominal pain or diarrhea. There are five viruses which affect the liver and cause hepatitis and five main types of viral hepatitis: Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), the Delta Hepatitis virus (HDV) [which only causes problems for people infected with HBV] and hepatitis E virus (HEV).[1]

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.[2] 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.[3] 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]

Most cases of acute HCV infection are asymptomatic.[4] Even when it is symptomatic, acute HCV infection tends to follow a mild course, with amino transferase levels rarely higher than 1000 U/L. Whether acute HCV infection is a cause of Fulminent Hepatic Failure remains controversial.

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.[5] 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. 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. For genotypes 2 and 3, the recommended treatment is PEG-IFN-α and ribavirin for 24 weeks.

In addition to the patient population that is not cured by the available regimens, there 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).[6,7,8] 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. 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.[9]

Sofosbuvir

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. Sofosbuvir work by reducing the amount of hepatitis C virus in the body, which may help in liver recover. Sofosbuvir is mainly used for the complete cure of the hepatitis C. Sofosbuvir based therapy presently provides a high cure rate, fewer side effects, and a two to four fold reduced duration of therapy. Numerous studies are either recruiting or active at present, evaluating sofosbuvir in different populations of patients and with different drug combinations for varying durations.[2]

The ultimate goal of hepatitis C treatment is prevention of hepatocellular carcinoma (HCC). The best way to reduce the long-term risk of HCC is to achieve sustained virological response (SVR). SVR is defined as an undetectable viral load at 12 weeks after treatment completion and indicates a cure. [] Currently available treatments include indirect and direct acting antiviral drugs. The indirect acting antivirals include pegylated interferon (PEG IFN) and ribavirin (RBV), which in combination have historically been the basis of therapy for HCV. Duration and response to these treatments varies based on genotype. These agents are poorly tolerated but are still used in some resource-poor areas and high-resource countries, they have been supplimented by direct acting antiviral agents, which first appeared in 2011; these agents target proteins responsible for viral replication and include the following three classes:

- NS3/4A protease inhibitors, including telaprevir, boceprevir, simeprevir, and others.
- NS5A inhibitors, including ledipasvir, daclatasvir, and others.
- NS5B polymerase inhibitors, including sofosbuvir, dasabuvir, and others.

These drugs are used in various combinations, sometimes combined with ribavirin, based on the patient's genotype (delineated as genotypes 1-6). Genotype 1 (GT1), which is the most prevalent genotype in the United States and around the world, can now be cured with a direct acting antiviral regimen. First-line therapy for GT1 is a combination of sofosbuvir and ledipasvir (SOF/LDV) for 12 weeks for most patients, including those with advanced fibrosis or cirrhosis. Certain patients with early disease need only 8 weeks of treatment while those with advanced fibrosis or cirrhosis who have not responded to prior treatment require 24 weeks. Cost remains a major factor limiting access to these drugs, particularly in low-resource nations; the cost of the 12-week GT1 regimen (SOF/LDV) has been estimated at US$94,500. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommend antiviral treatment for all patients with chronic hepatitis C infection except for those with additional chronic medical conditions that limit their life expectancy.[8]

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- methyl ethyl ester and a molecular formula of C2H29FN3O9P.[38] 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.[11] 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.[12]

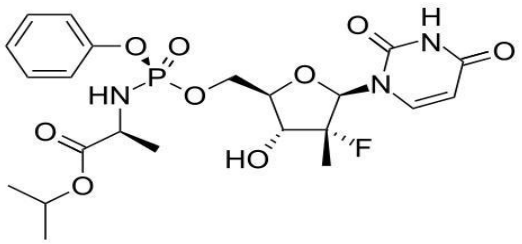

Figure 1: Molecular structure of sofosbuvir.

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).[12] 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 the metabolic pathway for activation of the prodrug is shown in figure.[13] The This analog then mimics the physiological nucleotide and competitively blocks the NS5B polymerase, thus inhibiting the HCV-RNA synthesis by RNA chain termination. The catalytic site of the enzyme is also highly conserved across all the genotypes, accounting for pan genotypic efficacy of sofosbuvir.[14]

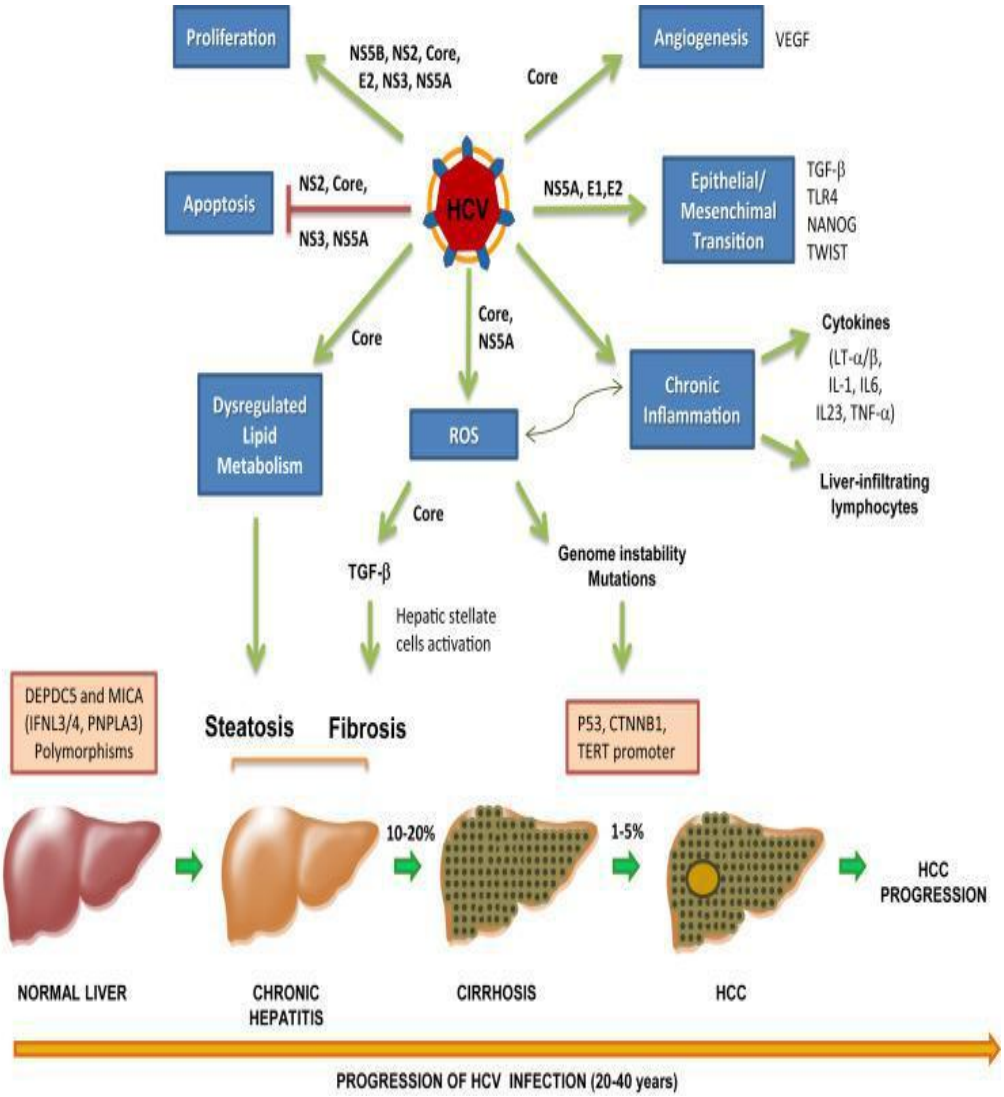

Figure 2: Mechanism of action.

Pharmacokinetics of sofosbuvir

Sofosbuvir to the compliance has a beneficial pharmacokinetic profile, being effectively orally as a single daily dose. This is likely to improve the compliances compared to protease inhibitors and PEG – IFN. Absorption and elimination where observed after single and multiple doses sofosbuvir. The metabolic activation of the prodrug take place by the enzymes present in the human liver. A systemic exposure of >90% is due to the metabolite GS-331007, which has also a longer tmax and elimination t1/2 than sofosbuvir.[15]

The effect of hepatic impairment was studied in 7-day treatment with sofosbuvir in 17 patients with moderate-to severe HCV related hepatic impairment compared to 8 non cirrhotic patients infected with HCV. There was no significant difference in the half life with or without hepatic impairment. The Cmax 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.[16]

The effect of the renal impairment on the pharmacokinetics of the sofosbuvir has also be studied with a single 400 mg dose, in patients with varying

degrees of renal impairment.[17] The AUC of an inactive nucleoside metabolites, PSI-6206, is increased by 56% in mild, 90% in moderate, and 456% in in severe renal impairment subjects, compared to normal subjects. Dosage or interval modifications are thus suggested in patients with moderate-to-severe renal impairmen.[18] Furthermore, 15% of sofosbuvir 53% of PSI-6206 have been extracted by hemodialysis in patients with end-stage renal diseases; dosage modification will be recommended in this group of patients.[19]

Adverse effect profile of sofosbuvir

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. No neutropenia, thrombocytopenia, or any serious adverse events are associated with sofosbuvir treatment.[20] 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.

Drug interaction 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.[21] 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.[11,14] 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.[22]

Resistence

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.[1,4,5,6]

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), thus indicating that sofosbuvir can be combined with other directly acting antiviral agents.[33] It has been suggested that additional mutations with amino acids change in both the finger and palm domains 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.[23]

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 400mg monotherapy or in combination with either ribavirin, PEG-INF or both.[24] 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.[25] 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.[26]

Efficacy

The efficacy and safety of sofosbuvir in patients with different HCV genotypes and with various combinations of drugs have been tested in various clinical trials. A dose of 400gm of sofosbuvir has been found to be more effective, with treatment duration ranging from 12 to 24 weeks, in various combinations of PEG-IFN and ribavirin in phase 2 clinical trials. 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% ($p< 0.001$).[15] Similar positive results have been found in numerous phase 3 clinical trials(table 1). Furthermore, recent phase1 and 2 studies of sofosbuvir in combination with other DAAs have also shown promising results.[27]

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.[28] 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).[5,6,7,12,13,14,15,23] 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).[5,6,7,12,13,14,15,23]

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).[29] 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.[30]

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.

REFERENCE

1. Wasley A, Grytdal S, Gallagher K, Centers for Disease Control and Prevention (CDC). Surveillance for acute viral hepatitis--United States, *MMWR Surveill Summ*, 2008 Mar 21; 57(2): 1-24.
2. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ Sofosbuvir for previously untreated chronic hepatitis C infection.N Engl J Med., 2013 May 16; 368(20): 1878-87.
3. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial.Kowdley KV, Lawitz E, Crespo I, Hassanein T, Davis MN, DeMicco M, Bernstein DE, Afdhal N, Vierling JM, Gordon SC, Anderson JK, Hyland RH, Dvory-Sobol H, An D, Hindes RG, Albanis E, Symonds WT, Berrey MM, Nelson DR, Jacobson IMLancet., 2013 Jun 15; 381(9883): 2100-7.
4. Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med*., 2008 Feb; 358(8): 811-827.
5. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat*, 2004 Mar; 11(2): 97-107.
6. Kowdley KV, Lawitz E, Crespo I, Hassanein T, Davis MN, DeMicco M, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): An open-label, randomised, multicentre phase 2 trial. Lancet, 2013; 381(21): 2–7.
7. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med, 2013; 368(18): 67–77.
8. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatit is C virus. *Nature*, 2009 Oct 8; 461(7265): 798-801.
9. Data from Phase 3 Studies of Gilead's Sofosbuvir for Hepatitis C to be Presented at 48thAnnual EASL Meeting; Findings Published Online in The New England Journal of Medicine. 2013. Apr, Available from: http://www.gilead.com/news/press-releases/2013/4/data-from-phase-3-studies-ofgileads-sofosbuvir-for-hepatitis-c.
10. Gentile I, Borgia F, Buonomo AR, Castaldo G, Borgia G. A novel promising therapeutic option against hepatitis C virus: An oral nucleotide NS5B polymerase inhibitor sofosbuvir. Curr Med Chem, 2013; 20(37): 33–42.
11. Highleyman L. DDW 2013: Interferon-free Simeprevir + Sofosbuvir SuppressesHepatitis C with or without Ribavirin. 2013. May, Available from:

http://www.hivandhepatitis.com/hepatitis-c/hepatitis-c-topics/hcv-treatment/4126-ddw-2013-interferon-free-simeprevir-sofosbuvir-suppresses-hepatitis-c-with-or-without ribavirin.
12. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med, 2013; 368: 34–44.
13. Soriano V, Vispo E, de Mendoza C, Labarga P, Fernandez-Montero JV, Poveda E, et al. Hepatitis C therapy with HCV NS5B polymerase inhibitors. Expert Opin Pharmacother, 2013; 14: 61–70.
14. Levin J. GS-7977 and HIV ARTs PK - No Clinically Significant Pharmacokinetic Interactions between Sofosbuvir (GS-7977) and HIV Antiretro virals Atripla, Rilpivirine, Darunavir/Ritonavir, or Raltegravir in Healthy Volunteers. AASLD- 63rd Annual Meeting of the American Association for the Study of Liver Diseases. 2012. Nov. Available from: http://www.natap.org/2012/AASLD/AASLD_64.htm.
15. http://www-ama-assn-org/resources/doc/usan/nabiximols.pdf.
16. Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection in Subjects with Chronic Genotype1,2,or3 HCV Infection.. Available from: http://clinicaltrials.gov/ct2/show/NCT01826981.
17. Murakami E, Tolstykh T, Bao H, Niu C, Steuer HM, Bao D, et al. Mechanism of activation of PSI-7851 and its diastereoisomer PSI-7977. J Biol Chem, 2010; 285: 34–47.
18. Krawitt EL.pharmacokinetics of sofosbuvir. *Am J Med*, 1994 Jan 17; 96(1A): 23S-26S.
19. http://www-ama-assn-org/resources/doc/usan/nabiximols.pdf.
20. Lam AM, Espiritu C, Bansal S, MicolochickSteuer HM, Niu C, Zennou V, et al. Genotype and subtype pro-ling of PSI-7977 as a nucleotide inhibitor of hepatitis C virus. Antimicrob Agents Chemother, 2012; 56(33): 59–68.
21. Murakami E, Tolstykh T, Bao H, Niu C, Steuer HM, Bao D, et al. Mechanism of activation of PSI-7851 and its diastereoisomer PSI-7977. J Biol Chem, 2010; 285: 34–47.
22. http://www.hcvdruginfo.ca/downloads/Hepatitis%20Cint_new%20nucleotide%20inhibitors.pdf.
23. An Open-Label Study of Sofosbuvir/Ledipasvir Fixed-Dose Combination in subjects with nosocomial genotype 1 HCV infection. Available from: http://clinicaltrials.gov/ct2/show/NCT01924949.
24. Open-Labeled Study of PSI-7977 and RBV with and without PEG-IFN in Treatment-naÏve Patients with HCV GT2 or GT3. Available from: http://clinicaltrials.gov/show/NCT01260350.
25. Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection in Subjects with Chronic Genotype1,2,or3 HCV Infection.. Available from: http://clinicaltrials.gov/ct2/show/NCT01826981.
26. Safety and Efficacy of Sofosbuvir/GS-5885 Fixed-dose Combination ± Ribavirin forthe Treatment of HCV (ION-2)]. Available from: http://clinicaltrials.gov/show/NCT01768286.
27. Rodriguez-Torres M, Lawitz E, Kowdley KV, Nelson DR, Dejesus E, McHutchison JG, et al. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naïve patients with HCV genotype 1: A randomized, 28-day, dose-ranging trial. J Hepatol, 2013; 58: 63–78.
28. Levin J. EASL 46th Annual Meeting. PROTON Study: PSI-7977 QD with PEG/RBV: 12-week Safety, RVR, cEVR, and SVR12 in Treatment-naÏve Patients with HCV GT2 or GT3 Available from: http://www.natap.org/2011/easl/easl_22.htm. http://clinicaltrials.gov/show/NCT01768286.
29. Krawitt EL.pharmacokinetics of sofosbuvir. *Am J Med*, 1994 Jan 17; 96(1A): 23S-26S.
30. Koneru A, Nelson N, Hariri S, et al. Increased activity of sofosbuvir.2011 *Morb Mortal Wkly Rep*., 2016 Jul 22; 65(28): 705-710.