ABSTRACT

Hepatitis C virus (HCV) is known to cause chronic hepatitis C, and its sequelae of cirrhosis and hepatocellular carcinoma. Hepatitis C genotype 3 (HCV-3) in particular is notorious for causing accelerated liver fibrosis, cardiovascular, and metabolic effects, thus increasing morbidity and mortality. It is the commonest variant in Asian countries like India and Pakistan. It is also one of the hardest-to-treat genotypes, especially among treatment-experienced and cirrhotic patients. Due to limited health care affordability and accessibility in these areas, many patients remain untreated.

Until recently, the established therapy for HCV had been a combination of pegylated interferon + ribavirin. However, it was only effective in about half of patients and had severe adverse effects; hence a more efficacious option needed to be found. Recent advances have led to the development of sofosbuvir, an NS5B inhibitor that is fast becoming the standard of care, in combination with other novel drugs. It was initially marketed at $1,000 per pill, a cost that was too high for most. Thus, it has not been utilized as a global therapy as yet. Formulation of effective interferon-free regimens is a huge milestone, and awareness needs to be raised regarding these new highly effective options in both the physician and the patient population.

This article discusses the newest drugs and combinations that have been developed in the fight against HCV-3, as a treatment outline for HCV-3-dominant areas. It also highlights recent breakthroughs in cost reductions of these drugs and the effort to make them globally accessible.

Keywords: Genotype 3, Hepatitis C, New therapies, Sofosbuvir.

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BACKGROUND

Hepatitis C virus (HCV) is notorious for causing liver cirrhosis and increasing the risk of hepatocellular carcinoma. In today's world of innovation, however, it is fast becoming a curable disease. The virus affects approximately 170 million people globally, of which about half are in Asia and the Western Pacific. It comprises seven genotypes, each with multiple subtypes. A total of 54.3 million cases are due to HCV genotype 3 (HCV-3), which is the most common variant in many parts of Asia, especially in India, Nepal, and Pakistan. Other areas where HCV-3 is more prevalent include Australia, Eastern and Western Europe, and Latin America. Some other genotypes commonly seen in Asia include HCV-1 and 2.

Hepatitis C virus genotype 3 has unique effects on glucose and lipid metabolism, causing the highest rate of virus-related liver steatosis out of all of the HCV types. The degree of steatosis correlates directly with HCV-RNA levels; hence eradication of the virus leads to a decrease in steatosis. It also carries a greater risk of cardiovascular disease and insulin resistance. It is notorious for an accelerated rate of liver fibrosis and an increased mortality compared with HCV-1 and 2, among patients who failed to achieve SVR (sustained virologic response) (Flow Chart 1 outlines these HCV-3-specific characteristics). Due to these alarming characteristics, there is an urgent need for adequate treatment options.

The previously established therapy for HCV-3 thus far had been pegylated interferon (pegIFN) (alpha-2a-180 mg/week or alpha-2b-1.5 mg/kg/week) + ribavirin (RBV) (800–1400 mg/day) for 24 weeks. However,
numerous studies have tried to determine the optimal treatment duration with varying results.\textsuperscript{15-17} Accepted durations included 12 weeks in patients achieving RVR (Rapid Virological Response) (treatment response at 4 weeks), but extending treatment to 36 weeks in those without RVR. Factors that complicate treatment include the presence of cirrhosis, high viral load, no RVR,\textsuperscript{18} and the presence of metabolic abnormalities. The EASL guidelines\textsuperscript{19} took all of these factors into account and thus recommended:

- Treatment for 16 weeks in patients with baseline low viral load (LVL) and RVR;
- At least 24 weeks of therapy in the presence of steatosis, advanced fibrosis, cirrhosis, or metabolic abnormalities like insulin resistance and metabolic syndrome;
- 48 or 72 weeks of treatment in those with early or delayed virologic response, given that HCV-RNA is undetectable at week 24;
- Discontinuation of treatment in those with no RVR, ≤2 \( \log_{10} \) drop in HCV-RNA levels or detectable RNA at week 24.

However, this interferon-based regimen was not without its drawbacks. In patients with HCV-3, SVR was achieved only in 33\% of cirrhotic patients, according to Aghemo et al, with a high posttreatment relapse rate.\textsuperscript{20} Furthermore, its use was limited by its wide range of adverse effects, including bone marrow depression, flu-like symptoms, neuropsychiatric disturbances, and autoimmune diseases. Occurrence of these symptoms had decreased the compliance with treatment and the willingness to initiate treatment with interferon.\textsuperscript{21} In some circumstances, use of pegIFN is contraindicated, including decompensated cirrhosis, Model for End Stage Liver Disease score >10, unstable psychiatric disorders, advanced cardiac or pulmonary disease, autoimmune diseases, and hematological abnormalities.\textsuperscript{22} These problems brought to light the necessity of developing interferon-free regimens and making them available for treatment worldwide, so we could take on the challenge of HCV, especially that of genotype 3.

This article highlights the current breakthroughs in treatment options for HCV-3, focusing on the new NS5B inhibitor sofosbuvir (SOF) and concurrent combinations, and recent advances that have been made in the effort to make these drugs globally accessible and cost-effective.

**CORNERSTONE OF THERAPEUTIC ADVANCES**

Sofosbuvir is an HCV-RNA NS5B inhibitor that blocks viral replication.\textsuperscript{23} It is a prodrug that is then converted within hepatocytes to its active form (GS-461203). This active form is then incorporated into HCV-RNA, causing chain termination.\textsuperscript{23,24} GS-461203 does not act on human DNA or RNA.\textsuperscript{25} It is then dephosphorylated to GS-331007, its circulating form, and excreted renally.\textsuperscript{23,24} It was approved by the FDA for use as the first nucleotide therapy against hepatitis C in December 2013 and subsequently was approved by the European Union in January 2014.\textsuperscript{26} Current AASLD guidelines now recommend the use of SOF + RBV for 24 weeks, or an alternative regimen of SOF + pegIFN + RBV for 12 weeks in all genotype 3 patients, as of March 2014.\textsuperscript{27} However, optimal treatment of HCV-3-infected patients is still largely unknown.\textsuperscript{28} Multiple clinical trials have been undertaken to assess the efficacy of different regimens in different patient populations, and to date, regimens with increased SVR rates and decreased side effects and resistance are still evolving.

**IFN-BASED THERAPIES**

The Lonestar-2 Trial assessed the use of SOF (400 mg OD) + pegIFN alpha-2a (180 µg once weekly) + RBV (1000 mg/day if <75 kg or 1200 mg/day if >75 kg – in two divided doses) for 12 weeks in treatment-experienced (TE) patients with HCV-2 or 3. The primary end point was SVR 12, which was achieved in 83\% of genotype 3 patients. The response was the same in cirrhotics and non-cirrhotics (83\% in both groups). There were four HCV-3 treatment failures; two patients had virologic relapse, and two were lost to follow-up. However, adverse effects occurred in a substantial number of patients in the study. The conclusion was that SOF + RBV + pegIFN for 12 weeks gave high SVR rates, regardless of cirrhosis.\textsuperscript{29}
**IFN-FREE REGIMENS**

**Sofosbuvir and Ribavirin**

The Electron trial was a phase II trial comparing different combinations of SOF and RBV with or without pegIFN. There were six treatment arms evaluating the optimal therapy for genotypes 2 and 3 in treatment-naive (TN) patients. They all contained combinations of these drugs for 12 weeks, except for arm 5, which tested SOF therapy alone for 12 weeks. All arms showed 100% SVR at week 12, except for SOF alone, which showed only 60% SVR12. The study concluded that SOF + RBV for 12 weeks was an effective treatment.30

The Fission trial compared the use of SOF (400 mg OD) + RBV (1000 mg/day if < 75 kg or 1200 mg/day if > 75 kg) for 12 weeks with use of pegIFN alpha-2a (180 μg once weekly) + RBV (fixed dose – 800 mg/day) for 24 weeks in TN chronic HCV-2 and 3 patients. In the SOF + RBV group, 99% patients had achieved SVR by week 4, and remained in remission at the end of treatment. However, SVR at 12 weeks post-therapy had decreased to 67%. Fifty-six percent of these were genotype 3 patients. In the pegIFN/RBV group, 67% patients had achieved SVR at week 4, 89% at the end of therapy, and only 67% remained in remission at week 12 post-therapy. Of these, there were 63% genotype 3 patients with SVR12. Of note, a higher response was seen in cirrhotic patients who were given SOF/RBV (47% with SVR12), in contrast to those given pegIFN/RBV (38% with SVR12). There was a drastic difference in the amount of adverse effects seen between the regimens, with an 11% discontinuation due to adverse effects in the interferon group, but only 1% in the SOF/RBV group. The study determined that SOF + RBV had similar efficacy to pegIFN + RBV, but had fewer side effects.31

The Valence study compared the effect of SOF + RBV in TN and TE chronic HCV-2 and 3 patients with placebo. For genotype 3, SOF (400 mg OD) and RBV (1000 mg/day if < 75 kg or 1200 mg/day if > 75 kg) were used for 24 weeks in 250 subjects, compared with 85 patients in the placebo group. SVR12 was 85% for HCV-3; 94% in the TN group and 79% in the TE group. Patients were then further subdivided based on cirrhosis and prior treatment. In TN group, 95% non-cirrhotics and 92% cirrhotics achieved SVR12, whereas in the TE group, 87% non-cirrhotics and only 62% cirrhotics achieved SVR12. No SVR was achieved in the placebo group. Thus, it was concluded that treatment with SOF/RBV for 24 weeks in HCV-3 achieved high SVR rates.32

Then came the Fusion trial. This assessed the efficacy of 12 weeks vs 16 weeks of therapy with SOF (400 mg OD) + RBV (1000 mg/day if < 75 kg or 1200 mg/day if > 75 g) in TE HCV-2 and 3 patients. Medication was given for 12 weeks, and then placebo for 4 weeks, in the first group, whereas the total treatment time was 16 weeks in the second group. At week 4, the SVR rates were 97 and 98% respectively. The end of the pertinent treatment period, both groups had achieved SVR of 100%. However, on follow-up at 12 weeks, SVR was only 50% in the first group of patients, while it was 73% in the latter group. For genotype 3 specifically, the SVR12 was 30% in the 12-week group, whereas it was 62% in the 16-week group. Further subdivision of HCV-3 patients showed that, for cirrhotics, SVR12 was 19% in the 12-week group, but 61% in the 16-week group. However, in non-cirrhotics, SVR12 was higher at 12 weeks, 37%, but similar to cirrhotics at 16 weeks, 63%. This proved an additional benefit of extending the treatment duration to 16 weeks.33

The Positron trial was undertaken to assess the effect of SOF (400 mg once daily) + RBV (1000 mg/day if < 75 g or 1200 mg/day if > 75 kg) vs placebo in HCV-2 and 3 patients in whom pegIFN was not an option (IFN-intolerant, unwilling, or ineligible). In both groups, patients were treated for 12 weeks. Sustained virologic response rates were 99% at week 4, 100% at week 12 (end of therapy), and 78% 12 weeks after the therapy ended. No SVR was achieved in the placebo arm. In genotype 3 patients, there was 61% SVR12. Further subdividing based on cirrhosis showed 68% SVR12 in non-cirrhotic HCV-3 patients vs 21% in cirrhotic HCV-3 patients. The study concluded that SOF + RBV was an effective option in this group, but that it was more effective in non-cirrhotics.33

**SOFOBUVIR, DACLATASVIR, AND ALISPORIVIR**

Daclatasvir (DCV) is a new, oral, highly selective NS5A inhibitor, with broad HCV coverage in vitro.34 Earlier this year, Sulkowski et al studied the combination of DCV + SOF in treating chronic hepatitis C. Their study in genotype 2 and 3 patients was divided into three arms for previously untreated patients. Arm 1, consisting of SOF for 7 days, then DCV + SOF for 23 weeks, showed an 83% SVR at the end of treatment. Arm 2, SOF + DCV for 24 weeks, had the most astounding results, with a 100% response at week 24. Finally, arm 3 had DCV + SOF with the addition of RBV for 24 weeks, and also showed a good response rate of 93% at week 24.35 Similarly, the recent ALLY-3 phase III study assessed the use of the RBV-free combination DCV 60 mg + SOF 400 mg QD for 12 weeks, in patients with chronic HCV-3. It showed SVR4 rates of 91% in TN and 86% in TE groups. Out of a total of 152 patients, only 15 had relapse posttreatment, 11 of which were cirrhotic. The combination was well tolerated. The results supported the use of 12 weeks of therapy, rather than the expected 24 weeks, in non-cirrhotic patients.36
These results showed promise for DCV as a very efficient future treatment option. Alisporivir is another new drug that inhibits cyclophilin-A–NS5A interactions, thus regulating many phases of the HCV replication cycle. García-Rivera studied the effect of Alisporivir in combination with NS5B inhibitors (SOF and Mercabamine) and NS5A inhibitors (DCV), and found it to have greater synergistic effects in HCV-3. Alisporivir monotherapy has been seen to cause adverse events. However, as mentioned above, very few pretreatment variants, there was a high response to 12 weeks of treatment with SOF thereafter. Therefore, it can be concluded that relapse after therapy is not due to SOF resistance.

Concerning DCV, Sulkowski et al’s study demonstrated resistance polymorphisms in 5 of 18 genotype 3 patients. Pretreatment polymorphisms known to have caused loss of susceptibility to DCV in vitro, such as NS5A-A30K, were isolated. However, four of these five patients had a sustained virologic response.

Alisporivir has been seen to have a high barrier to resistance. Viral breakthrough was seen only in patients with non-CC IL-28B allele and was associated with low drug dosage. In patients treated with SOF + GS-5816, Doehle et al showed that despite the presence of preexisting NS5A resistance associated variants (RAV’s) in 12 out of 54 HCV-3 cases, 9 did achieve SVR. These included the A30K and Y93H variants. The study concluded that despite the existence of these pretreatment variants, there was still a very high response to 12 weeks of treatment with GS-5816.

PERI-TRANSPLANTATION PERIOD

The use of SOF (400 mg OD) and RBV (weight based; 1000 mg/day if <75 kg, 1200 mg/day if >75 kg) in the peri-transplantation period, for 24 to 48 weeks or until the time of transplant, was proven by Curry et al to prevent HCV recurrence post-transplantation in 70% of patients who had undetectable HCV-RNA prior to transplant.

This, in comparison to the previous response rate of 29% in HCV-3 patients treated with pegIFN and RBV pretransplantation, was a major milestone. For post-transplantation therapy, the AASLD recommends the use of SOF 400 mg + RBV starting at 600 mg, and bringing the dose up to the weight-based regimen slowly, for 24 weeks, in compensated HCV-3 cases.

SOFOSBUVIR IN SPECIAL CIRCUMSTANCES

HIV/HCV Co-infection

HIV co-infection is known to cause faster progression to fibrosis and a poorer long-term outcome. Sofosbuvir is the first DAA (direct-acting antiviral) to be FDA approved for use in HIV/HCV co-infection. The use of SOF + RBV for 24 weeks in this population showed 67% SVR for HCV-3. The AASLD recommends the use of SOF 400 mg OD + RBV weight based (same as for HCV mono-infected patients) for 24 weeks, in HCV-3/HIV co-infected patients.
RENAI AL FAILURE

Use of SOF and other DAA-based regimens becomes an issue when the GFR falls below 50 mL/min. The AASLD says that no dosage changes are required if GFR > 30 mL/min, but does not recommend SOF use if GFR < 30 mL/min, or if the patient is on hemodialysis. However, guidelines have not yet been established for an ideal alternative therapy in this population.

HEPATIC IMPAIRMENT

In patients with mild-to-moderate hepatic impairment, raised SOF levels were seen. However, cirrhosis did not significantly alter its pharmacokinetics. No dosage adjustment is recommended in mild, moderate, or severe hepatic impairment. Concerning SOF in decompensated cirrhosis, guidelines have not yet been established.

CURRENT COSTS AND DRUG AVAILABILITY

Currently, SOF, produced by Gilead as Sovaldi®, has been marketed at a price of $1,000 per pill or $84,000 for the whole 12-week course of medication, and costs are further increased by the need for drug combinations. This has made the drug inaccessible for thousands of people suffering from HCV worldwide, especially in countries with poor health care systems in place and where patients have to pay the whole cost from their own pockets. This has been a very distressing issue for both the physician and the patient population globally. Many civil society organizations and agencies have advocated that the price of this new medication be reduced to $500 per course, but as of yet, this has not happened. The WHO recently issued a statement urging price reduction for new medications like SOF, so that they can be used on a large scale.

Egypt, at 14% HCV-affected population, has the highest prevalence in the world and has made headway in securing the whole course of SOF at $900 for a 12-week course. In France, the price of the 12-week course has been brought down to 41,000 euros ($51,373), thanks to the Economic Committee for Health Products (CEPS). In September 2014, Gilead has signed a deal with seven Indian pharmaceutical companies for them to develop SOF, and the single-tablet ledipasvir/SOF combination, for distribution in 91 developing countries (Table 1) at $10 per pill or $900 for the 12-week course (Table 2 gives a comparison of HCV-3 drug costs). Asian countries included in this deal are Pakistan, India, Afghanistan, Bangladesh, Bhutan, Cambodia, Indonesia, Laos, Kyrgyz Republic, Maldives, Mongolia, Myanmar, Nepal, North Korea, Sri Lanka, Tajikistan, Turkmenistan, Uzbekistan, and Vietnam. For the first time, patients in these countries

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**Table 1: Countries included in Gilead’s generic manufacturing and distribution deal**

| Afghanistan | Chad | Comoros | Guatemala | Guinea | Maldives | Mali | Samoa | Rwanda | Swaziland | Tajikistan | Tanzania | Timor Leste | Togo | Tonga | Tuvalu | Uganda | Uzbekistan | Vanuatu | Vietnam | Zamb | Zimbabwe |
|-------------|------|---------|-----------|-------|---------|-----|-------|--------|----------|-----------|---------|-----------|-----|------|-------|--------|-------------|--------|--------|-------|----------|
will have a chance to fight HCV with these new, highly effective drugs. Awareness needs to be raised about the availability, and now cost-effectiveness, of this treatment option, as it could have a considerable impact on the global disease burden and economy.

Daclatasvir, produced by Bristol-Meyers-Squibb as Daclina®9, has been approved by the European Commission for use in HCV-infected patients. It should soon be on the international market and its use should be incorporated into novel treatment regimens in Asia once that happens. GS-5816 is still in trials, and physicians and practitioners should keep this drug in mind as a highly effective therapy as well.

**FUTURE NEEDS**

Focus on future therapeutic development needs to be on an even lower occurrence of adverse effects, improved treatment efficacy in TE and cirrhotic patients, and use of drugs with a high barrier to resistance.

Of note, Simeprevir and the “Abbvie” regimen have not yet been proven to be effective in genotype 3 HCV-affected patients. More studies need to be undertaken with these drugs in order to establish a conclusive benefit, harm, or non-effect in HCV-3-affected patients.

**REFERENCES**

1. Deinestang JL, McHutchinson JG. American Gastroenterological Association technical review on the management of hepatitis C. Gastroenterology 2006 Jan;130(1):231-264.
2. World Health Organization. Hepatitis C. Available from: http://www.euro.who.int/en/what-we-do/health-topics/communicable-diseases/hepatitis.
3. Simmonds P, Bukh J, Combet C, Deléage G, Enomoto N, Feinstone S, Halfon P, Inchauspé G, Kuiken C, Maertens G, et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 2005 Oct;42(4):962-973.
4. Messina JP, Humphreys J, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015 Jan;61(1):77-87.
5. Negro F. Steatosis and insulin resistance in response to treatment of chronic hepatitis C. J Viral Hepat 2012 Jan;19 (Suppl 1):42-47.
6. Jhaveri R, McHutchison J, Patel K, Qiang G, Diehl AM. Specific polymorphisms in hepatitis C virus genotype 3 core protein associated with intracellular lipid accumulation. J Infect Dis 2008 Jan 15;197(2):283-291.
7. Poynard T, Ratziu V, McHutchison J, Manns M, Goodman Z, Zeuzem S, Younossi Z, Albright J. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. Hepatology 2003 Jul;38(1):75-85.
8. Patton HM, Patel K, Behling C, Bylund D, Blatt LM, Vallée M, Heaton S, Conrad A, Pockros PJ, McHutchison JG. The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients. J Hepatol 2004 Mar;40(3):484-490.
9. Younossi ZM, Stepanova M, Nader F, Younossi Z, Elsheikh E. Associations of chronic hepatitis C with metabolic and cardiac outcomes. Aliment Pharmacol Ther 2013 Mar;37(6):647-652.
10. Hui JM, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, McCaughan GW, George J. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. Gastroenterology 2003 Dec;125(6):1695-1704.
11. Moucari R, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, Sobesky R, Martinot-Peignoux M, Maylin S, Nicolas-Chanoine MH, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. Gastroenterology 2008 Feb;134(2):416-423.
12. Bochud PY, Cai T, Overbeck K, Bochud M, Dufour JF, Müllhäupt B, Borovicka J, Heim M, Moradpour D, Cerny A, et al. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C J Hepatol 2009 Oct;51(4):655-666.
13. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011 Jun;9(6):509-516.
14. Ghanéy MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009 Apr;49(4):1335-1374.
15. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albright JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001 Sep 22;358(9286):958-965.
16. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinus G, González FI Jr, Häussinger D, Diago M, Carosi G, Dumeaux D, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002 Sep 26;347(13):975-982.
17. Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, Vinelli F, Scotto G, Bacca D, Annese M, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med 2005 Jun 23;352(25):2609-2617.
18. Scherzer TM, Hofer H, Staettermayer AF, Rutter K, Beinhardt S, Steindl-Munda P, Kerschner H, Kessler HH, Ferenci P. Early virologic response and IL28B polymorphisms in patients with chronic hepatitis C: association with genotypes 1 and 4. J Hepatol 2011 May;54(5):866-871.
19. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011 Aug;55(2):245-264.
20. Aghemo A, Rumi MG, Monico S, Prati GM, D’Ambrosio R, Donato MF, Colombo M. The pattern of pegylated interferon-alpha2b and ribavirin treatment failure in cirrhotic patients depends on hepatitis C virus genotype. Antivir Ther 2009;14(4):577-584.
21. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut 2006 Sep;55(9):1350-1359.
22. Ghanéy MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009 Apr;49(4):1335-1374.
Tackling HCV-3 in Asia: Breakthroughs for Efficient and Cost-effective Treatment Strategies

23. Keating GM. Sofosbuvir: a review of its use in patients with chronic hepatitis C. Drugs 2014 Jul;74(10):1127-1146.

24. European Medicines Agency. Sovaldi (sofosbuvir): EU summary of product characteristics. 2014. [Accessed 2014 Mar 31]. Available from: http://www.ema.europa.eu/.

25. Arnold JJ, Sharma SD, Feng YJ, Ray AS, Smidansky ED, Kireeva ML, Cho A, Perry J, Vela JE, Park Y, et al. Sensitivity of mitochondrial transcription and resistance of RNA polymerase II dependent nuclear transcription of antiviral ribonucleosides. PLoS Pathog 2012;8(11):e1003030.

26. Jacobson IM, Gordon SC, Kowdle KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013 May 16;368(20):1867-1877.

27. American Association for the Study of Liver Diseases. Recommendations for testing, managing and treating hepatitis C. Available from: http://www.hcvguidelines.org/full-report.

28. Pawlotsky JM. New hepatitis C therapies: the toolbox, strategies, and challenges. Gastroenterology 2014 May;146(5):1176-1192.

29. Lawitz E, Poordad F, Brainard DM, Hyland RH, An D, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir in combination with peg-IFN and ribavirin for 12 weeks provides High SVR rates in HCV infected genotype 2 or 3 treatment experienced Patients with and without compensated cirrhosis: results from the LONESTAR-2 study. Hepatology 2013 Nov 26;58(Suppl 6):Abstract LB-4.

30. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013 Jan 3;368(1):34-44.

31. Lawitz E, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013 Aug 15;369(7):678-679.

32. Zeuzem S, Dusheiko GM, Salumerre R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, et al. Sofosbuvir and Ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014 May 22;370(21):1993-2001.

33. Jacobson IM, Gordon SC, Kowdle KY, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013 May 16;368(20):1867-1877.

34. Friddell RA, Qiu D, Valera L, Wang C, Rose RE, Gao M. Distinct functions of N5SA in hepatitis C virus RNA replication uncovered by studies with theN5SA inhibitor BMS-790052. J Virol 2011 Jul;85(14):7312-7320.

35. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson L, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014 Jan 16;370(3):211-221.

36. Nelson DR, Cooper JN, Lalazari JP, Lawitz E, Pockros P, Freilich BF, Younes ZH, Harlan W, Ghalib R, Oguchi G, et al. All oral 12 week combination treatment with Daclatasvir (DVC) and Sofosbuvir (SOF) in patients infected with HCV genotype (GT) 3: ALLY-3 Phase 3 study. Hepatology 2014;60(Suppl 4):Abstract LB-3.

37. Gallay PA, Lin K. Profile of Alisporivir and its potential in the treatment of hepatitis C. Drug Des Dev Ther 2013;7:105-115.

38. Ampuero J, Romero-Gómez M, Reddy KR. Review article: HCV genotype 3 – the new treatment challenge. Aliment Pharmacol Ther 2014 Apr;39(7):686-698.

39. Chatterji U, Garcia-Rivera JA, Baugh J, Gavlik K, Wong KA, Zhong W, Brass CA, Naoumov NV, Gallay PA. The combination of alisporivir plus an NS5A inhibitor provides additive to synergistic anti-hepatitis C virus activity without detectable cross-resistance. Antimicrob Agents Chemother 2014 Jun;58(6):3327-3334.

40. Everson GT, Tran TT, Towner WJ, Davis MN, Wyles D, Nahass R, McNally J, Brainard DM, Han L, Doehle B, et al. Safety and efficacy of treatment with the interferon-free, ribavirin-free combination of sofosbuvir +GS-5816 for 12 weeks in treatment-naive patients with genotype 1-6 HCV infection. J Hepatol 2014 Apr;60(1):546.

41. Gane EJ, Hyland RH, An D, Svarovskaia E, McNally J, Brainard DM, Symonds WT, McHutchison JG, Stedman CA. Once daily sofosbuvir with GS-5816 for 8 weeks with or without ribavirin in patients with HCV genotype 3 without cirrhosis result in high rates of SVR12: the ELECTRON-2 study. Hepatology 2014 Oct;60(Suppl 4):A79.

42. Tran TT, Morgan MR, Thuluvath PJ, Etzkorn K, Hinestrosa F, Tong M, McNally J, Brainard DM, Han L, Doehle B, et al. Safety and efficacy of treatment with sofosbuvir + GS5816 x ribavirin for 8 or 12 weeks in treatment naive patients with genotype 1-6 HCV infection. Hepatology 2014 Oct;60(Suppl 4):A80.

43. German P, Moorehead L, Pang PS, Vimal M, Mathias A. Lack of a clinically significant pharmacokinetic interaction between norgestimate/ethinyl estradiol and sofosbuvir (SOF) or ledipasvir (LDV) in HCV-uninfected female subjects [abstract no. 469]. Hepatology 2013;58(Suppl 4):E33A.

44. Mogalian E, German P, Brainard DM, Link J, McNally J, Han LL, Kearney B. Lack of a clinically significant pharmacokinetic drug-drug interaction between sofosbuvir and GS-5816 in healthy volunteers [abstract no. 465]. Hepatology 2013;58(Suppl 4):E31A.

45. Mathias A, Compropiot M, Clemons D, Denning J, Symonds WT. No clinically significant pharmacokinetic drug-drug interactions between sofosbuvir (GS-7977) and the immunosuppressants, cyclosporine A or tacrolimus in healthy volunteers [abstract no. 1869]. Hepatology 2012;56(Suppl 4):1063A-1064A.

46. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013 Jan 3;368(1):34-44.

47. Svarovskaia ES, Dvoy-Sobol HS, Hebner C, Doehle B, Gontcharova V, Martin R, Gane EJ, Jacobson IM, Nelson DR, Lawitz E, et al. No resistance detected in four phase 3 clinical studies in HCV genotype 1-6 of sofosbuvir/ribavirin with or without peginterferon [abstract no. 1843]. Hepatology 2013;58(Suppl 4):1091A-1092A.

48. Doehle B, Gontcharova V, Chodavarapu RK, McNally J, Chung RT, Everson GT, McHutchison JG, Miller MD, Mo H. Resistance analysis of treatment-naïve HCV genotype 1-6 infected patients treated with sofosbuvir in combination with GS-5816 for 12 weeks. Hepatology 2014 Oct;60(Suppl 4):A1942.

49. Curry MP, Forns X, Chung RT, Tarrailt NA, Brown RJr, Fenkel JM, Gordon F, O'Leary J, Kuo A, Schiano T, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open label study. Gastroenterology 2015 Jan;148(1):100-107.

50. Everson GT, Tarrailt NA, Lok AS, Rodrigo del R, Brown RS Jr, Saab S, Shiffman ML, Al-Osaimi AM, Kulik LM, Gillespie BW, et al. A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis C after liver transplantation. Hepatology 2013 May;57(5):1752-1762.
51. Degasperi E, Aghemo A. Sofosbuvir for the treatment of chronic hepatitis C: between current evidence and future perspectives. Hepat Med 2014 Apr 29;6:25-33.
52. Sulkowski MS, Naggie S, Lalezari J, Fessel WJ, Mounzer K, Shuhart M, Luetkemeyer AF, Asmuth D, Gaggar A, Ni L, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV Coinfection. JAMA 2014 Jul 23-30;312(4):353-361.
53. Kirby B, Gordi T, Symonds WT, Kearney BP, Mathias A. Population pharmacokinetics of sofosbuvir and its major metabolite (GS-331007) in healthy and HCV infected adult subjects [abstract no. 1106]. Hepatology 2013;58(Suppl 4):746A-747A.
54. Phelan M, Cook C. A treatment revolution for those who can afford it? BMC Infect Dis 2014;14 (Suppl 6):S5.
55. WHO. Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva; 2014. Available from: http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf.
56. Esmat G. Hepatitis C in the Eastern Mediterranean Region. East Mediterr Health J 2013 Jul;19(7):587-588.
57. Breban R, Arafa N, Leroy S, Mostafa A, Bakr I, Tondeur L, Abdel-Hamid M, Doss W, Esmat G, Mohamed MK, et al. Effect of preventive and curative interventions on hepatitis C virus transmission in Egypt (ANRS 1211): a modelling study. Lancet Glob Health 2014 Sep;2(9):e541-e549.

58. HCV New Drug Research. France pegs Gilead hepatitis C drug at “lowest price in Europe”. Reuters; 2014 Nov. Available from: http://www.reuters.com/article/2014/11/20/health-hepatitis-gilead-solvadi-idUSL6N0TA2TA20141120.
59. Gilead Sciences Inc. Chronic hepatitis C treatment expansion generic manufacturing for developing countries. 2014 Sep. Available from: http://www.gilead.com/-/media/other/HCVGenericAgreementFactSheet.pdf.
60. Gokhale K. Gilead in talks to offer cheaper sofosbuvir to 80 countries. PharmaEconomicsOutcomes News 2014 Sep;711(1):2.
61. ReauNS,JensenDM,Stickershock and the price of new therapies for hepatitis C: is it worth it? Hepatology 2014 Apr;59(4):1246-1249.
62. Cha A, Budovich A. Sofosbuvir: a new oral once daily agent for the treatment of hepatitis C virus infection. PT 2014 May;39(5):345-352.
63. Poole RM. Daclatasvir + asunaprevir: first global approval. Drugs 2014 Sep;74(13):1559-1571.
64. Lawitz E, Sullivan G, Rodriguez-Torres M, Bennett M, Poordad F, Kapoor M, Badri P, Campbell A, Rodrigues L Jr, Hu Y, et al. Exploratory trial of ombitasavir and ABT-450/r with or without ribavirin for HCV genotype 1,2 and 3 infection. J Infect 2015 Feb;70(2):197-205.
65. You DM, Pockros PJ. Simeprevir for the treatment of chronic hepatitis C. Expert Opin Pharmacother 2013 Dec;14(18):2581-2589.