

Next Generation Direct-acting Antiviral Agents for Hepatitis C Treatment

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Sofosbuvir in combination with peginterferon and ribavirin for 12 weeks is a new treatment paradigm with a 12 week course of therapy leading to high sustained response rates in genotype 1 and 4 infected individuals including high sustained response rates in cirrhotic patients. In addition, genotype 2 and 3 infected individuals now have an all oral regimen of sofosbuvir and ribavirin, which is highly effective in all genotype 2 infected individuals with 12 weeks of therapy. For genotype 3 infected individuals, 24 weeks of the sofosbuvir and ribavirin leads to high sustained virological response rates in most groups. However, cirrhotic genotype 3 infected individuals are going to require additional strategies to optimize SVR rates. It is expected that 2014 should see the presentation of phase 3 data with a variety of combinations of direct acting antiviral agents with the anticipated approval of these combinations occurring in late 2014 or early 2015. Moreover, one should expect that SVR rates above 90% for treatment naive and treatment failure patients should be the expected norm for all patients.

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INTRODUCTION

The Hepatitis C virus (HCV) is of the most common blood born infections worldwide, and is a major cause of chronic liver disease leading to death from liver failure or hepatocellular carcinoma.¹ Until 2011, the current paradigm for HCV treatment relied on pegylated interferon and ribavirin as agents that enhance endogenous mechanisms for viral clearance and are dependent on host factors. In patients with genotype 1 HCV infection, which comprises the majority of patients infected in many parts of the world, including Asia, North America, and Europe, sustained viral response (SVR) rates remained suboptimal with less than half of genotype 1 infected individuals going on to achieve SVR. In May 2011, two NS3 protease inhibitors, boceprevir and telaprevir, were approved in combination with peginterferon and ribavirin for the treatment of chronic hepatitis C, genotype 1. These agents, known as direct acting antiviral agents (DAAs) represented a major advance in the treatment of genotype 1 hepatitis C with sustained response rates (SVR) of 63-75%, significantly better than the previous standard of care, pegylated interferon and ribavirin. Treatment duration could be truncated in half of patients from 24 to 48 weeks. However, associated with these higher SVR rates were additional side effects including anemia and rash. And still, many of these infected with hepatitis C cannot tolerate the pegylated interferon and ribavirin backbone required for successful therapy. However, these advances have led to a shift in the investigational focus for

treatment of HCV towards direct acting anti-viral agents (DAA) with the goal of eliminating interferon and ribavirin, as well as further truncating treatment duration to provide more effective and better tolerated therapies. In this mini-review we will cover the next generation of DAA agents for hepatitis C demonstrating that high SVR rates can be achieved in all populations with therapies that are well tolerated.

Prior to reviewing the new antiviral agents that are in development, it is important to know the key characteristics of the different classes of direct-acting antiviral agents and what targets are inhibited in the hepatitis C genome. The Hepatitis C virus is a single-stranded RNA molecule that is approximately 9,600 nucleotides in length. The hepatitis C life cycle is similar to many positive strand RNA viruses. The virus enters the cell through attachment entry and fusion and undergoes transcription to form a complementary negative sense RNA molecule which serves as the template for positive stranded RNA molecules. This HCV RNA reading frame contains approximately 9000 nucleotides and generates 3 structural proteins, 6 nonstructural proteins, and 2 proteins of unclear function. The structural proteins are used to assemble new viral particles and the NS proteins support viral RNA replication. The NS3/4A is a serine protease (NS3) and cofactor (NS 4A) that catalyzes the post-translational processing of NS proteins from the polyprotein which is important for viral replication. The NS3 protease cleaves NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions. The initial therapies in the direct-acting antiviral drug development were directed toward the NS3 protease (boceprevir and telaprevir). These first generation protease

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inhibitors have high potency, but limited genotypic coverage and a lower barrier to resistance. After translation, HCV RNA replication primarily depends upon the RNA dependent/RNA polymerase (NS5B). X-ray crystallography has demonstrated that the NS5B polymerase has a classical fingers, palm, and thumb structure providing multiple areas for therapeutic targets, which are currently in development. Nucleoside and nucleotide inhibitors that bind the active site of the NS5B hepatitis C polymerase and terminate replication show intermediate to high potency are pan genotypic. The main advantage of using this class relates to a very high barrier to resistance due to the low replicative fitness of resistant variants. Sofosbuvir is a polymerase inhibitor, recently approved that binds to the catalytic site. Non-nucleoside inhibitors (NNI) bind to different parts of the polymerase not involving the catalytic site, do not act as chain terminators, and have intermediate potency and limited genotypic coverage. Their barrier resistance is lower. Another key structure in HCV replication is the NS5A protein, which has a key role in formation of the replication complex as well as interacting with the NS5B polymerase. Multiple NS5A inhibitors will be introduced in the next year as part of a multi DAA regimen. Thus, in our assembly of therapeutic strategies for hepatitis C, one can use a combination of interferon, ribavirin with NS3 inhibitors, NS5A inhibitors, NS5B inhibitors, and NS5B non-nucleoside polymerase inhibitors (**Figure 1**). In December 2013, the approval of additional protease inhibitor, simeprevir, in combination with the approval of the nucleotide polymerase inhibitor, sofosbuvir, has again advanced the treatment of hepatitis C and ushered in the first era of all oral therapy for genotypes 2 and 3. In addition, the simeprevir is a second-wave protease inhibitor with an improved side effect profile, which when added to peginterferon and ribavirin leads to high sustained response rates.

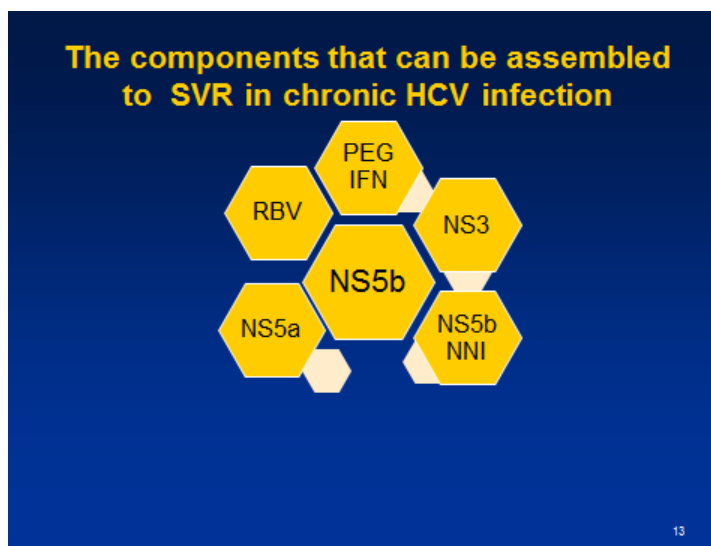


Figure 1. A variety of therapeutic strategies combining multiple DAAs with or without interferon and ribavirin may be used to achieve SVR.

NEW THERAPIES

Genotype 1 Treatment, Next Generation Direct-Acting Antiviral Agents

NS3 Protease inhibitors in combination with Peg interferon and ribavirin

In December 2013, the approval of the NS3 protease, simeprevir was announced by the US Regulatory Authorities in combination with peginterferon and ribavirin. Simeprevir is a once daily HCV protease inhibitor with an improved side effect profile with no anemia as compared to the initially approved protease inhibitors, boceprevir and telaprevir.

Simeprevir was approved in combination with peginterferon and ribavirin for naïve and previous peg interferon ribavirin treatment failure patients. The approval was based on the phase 3 Quest 1 and Quest 2 studies, which demonstrated high sustained virologic response of 80% compared to the control arm SVR rate of 50%.^{2,3} In addition, 88% of individuals treated were able to be treated for just 24 weeks with a high sustained virologic response rate. Complicating this was a lower sustained response rates in individuals with the pre-existing Q80K polymorphism at baseline. This polymorphism occurs predominantly in genotype 1a individuals (and is rare in genotype 1b). Sustained virologic response rates were lower (genotype 1a Q80K positive 58%, Q80K 1a negative 75%) compared to genotype 1b, where sustained virologic response rates were above 80%. The regulatory authorities have recommended pre-therapy testing for the Q80K polymorphism as the prevalence of Q80K mutations was approximately 29.5% in the genotype 1a population with due to the high prevalence in North America.

A second protease inhibitor, faldaprevir is also an NS3 protease inhibitor with daily dosing and an improved side effect profile without anemia. A pooled analysis from Phase 3 results in treatment naïve patients (STARTVerso™1&2 trials) treated with with faldaprevir 120 mg or 240 mg in combination with peg interferon and ribavirin demonstrated SVR rates of 72-73% with 84% of individuals qualifying for short duration therapy.³ Unlike with simeprevir based therapy, SVR rates were not affected with the Q80K polymorphism in the genotype 1a population. It is anticipated that faldaprevir will be available with peg interferon and ribavirin in the next year.

NS5B POLYMERASE INHIBITORS IN COMBINATION WITH PEG INTERFERON AND RIBAVIRIN FOR GENOTYPES 1 AND 4

The next new class of medicine to be approved for treatment of hepatitis C is sofosbuvir, a HCV specific nucleotide polymerase inhibitor (chain-terminating), which shows potent antiviral activity against genotypes 1 through 6.⁴ It is also dosed once daily and as nucleotide polymerase inhibitor is excreted in the urine with no significant food effects and no significant drug-drug interactions, specifically no cytochrome P450 interactions. In the phase 3 registration trial (Neutrino), 12 weeks of sofosbuvir, peginterferon, and ribavirin led to an overall sustained response rate of 90% with a genotype 1 sustained virologic response rate of 89%.⁵

Small cohorts of genotypes 4, 5, and 6 were included and the sustained response rates were 96% and 100% respectively. By fibrosis stage, SVR rates ranged from 100% with F0 to 78% with cirrhosis. Currently, sofosbuvir has been approved by the regulatory authorities for hepatitis C genotype 1 and 4 infection in combination with peginterferon and ribavirin for 12 weeks. This truncates the treatment duration from 24 to 48 weeks with the previous generation protease inhibitors in combination with peg interferon and ribavirin to 12 weeks with sustained virologic response rates, which are numerically higher and with a markedly reduced side effect profile.

Preliminary Data: Polymerase Inhibitor with Other Agents for Genotype 1

Sofosbuvir may also be administered with ribavirin or with other direct acting antiviral with or without ribavirin agents for genotype 1 infection. Results from the Electron study and ongoing study for genotype 1 hepatitis C, sofosbuvir was combined with ribavirin, the NS5A inhibitor, ledipasvir, with ribavirin or with the non-nucleoside polymerase inhibitor GS-9669.⁶ With just sofosbuvir monotherapy and ribavirin for 12 weeks in the initial Electron study cohort, an overall SVR rate of 84% was achieved.⁷ This, in combination with other data has led to the approval of sofosbuvir and ribavirin for 24 weeks for genotype 1 infected individuals in patients who cannot tolerate interferon based therapies.

The addition of ledipasvir with ribavirin or GS-9669 with ribavirin also led to high sustained response rates of 100% and 92% respectively. Additional cohorts in the Electron study examined sofosbuvir and ledipasvir without ribavirin for 12 weeks as well as in cirrhotic patients who had failed therapy with peginterferon and ribavirin. In these cohorts, the combination of sofosbuvir and ledipasvir without ribavirin in cirrhotic led to an overall sustained response rate of 70% with the addition of ribavirin increasing the SVR rate to 100%. Similarly, the addition of ledipasvir with sofosbuvir and ribavirin in F3-F4 cohorts led to an SVR rate of 100% in the phase 2 Lonestar study, including those who failed triple therapy with telaprevir or boceprevir.⁸ The phase 3 sofosbuvir based trials will be reported in early 2014.

Sofosbuvir may be combined with NS3 protease inhibitors including simeprevir with high sustained virologic responses rates. In the COSMOS study, simeprevir and sofosbuvir were combined for 12 or 24 weeks with and without ribavirin.⁹ The 12-week cohorts have now been reported for genotype 1 individuals who are treatment naive as well as null responders. The SVR 12 rates in naive patients were very high (100%) in treatment naive individuals and the SVR4 rates in advanced fibrosis patients who were both naive and null responders ranged from 93% to 100%. The final SVR reports are eagerly awaited. In addition, sofosbuvir has now been combined with daclatasvir, another NS5A inhibitor.¹⁰ In this pilot study of 211 F0 to F2 individuals genotype 1 infected individuals including treatment naive individuals who received 12 weeks of sofosbuvir and daclatasvir with or without ribavirin and treatment failure individuals, including protease inhibitors,

who received 24 weeks of sofosbuvir and daclatasvir, SVR rates were 98% in both groups. Thus the combination of sofosbuvir with multiple classes of DAA agents can lead to high SVR rates in all individuals including those who failed first generation protease inhibitors with peginterferon and ribavirin.

Treatment with DAA Combinations without Polymerase Inhibitor in Genotype 1 Patients

High SVR rates may also be seen without the backbone nucleotide or nucleoside polymerase inhibitor. Preliminary data from a recent phase 2 study (Aviator) examined the efficacy of combinations of the NS3 protease inhibitor, ABT-450 with the NS5A inhibitor ABT-267, and non-nucleoside polymerase inhibitor ABT-333 with ribavirin in 571 noncirrhotic naive and null-responders for 12 and 24 week durations.¹¹ The highest SVR rates were noted when all 3 DAAs were combined with ribavirin. The sustained response rate ranged from 96% in naive patients and 93% in null responders with 12 weeks of therapy respectively. The phase 3 program is well underway with results expected in early 2014.

For genotype 1b infected individuals in Asian countries such as Japan where the population is predominantly genotype 1b, the all oral combination of NS5A combination of daclatasvir with NS3 protease inhibitor asunaprevir has been shown to lead to high sustained response rates.¹² In a phase 3 study, 222 Japanese subjects who received twenty-four weeks of daclatasvir plus asunaprevir led to SVR 24 rates 87.4% in interferon ineligible intolerant individuals and 80.5% of individuals who were null responders. The efficacy of combining a protease inhibitor with a NS5A inhibitor was also replicated in a pilot study of with ABT-450 plus ABT-267 for 12 weeks where a high sustained response rates in 40 genotype 1b naive patients of 95% was noted with null responders- achieving an overall SVR rate of 90% with 12 weeks of therapy.¹³ Another genotype 1b treatment strategy includes the combination of the NS3 protease inhibitor faldaprevir in combination with the nonnucleoside inhibitor deleobuvir with ribavirin.¹⁴ Sustained response rates ranged from 52-69% with markedly higher SVR rates in genotype 1b individuals. It is important to note that many of these high sustained virologic response rates were achieved without the use of ribavirin in genotype 1b individuals suggesting that not only elimination of interferon is available but treatments are evolving toward the elimination of ribavirin.

Daclatasvir, asunaprevir and the non-nucleoside polymerase inhibitor, BMS-791325 has also shown promise. In a phase 2 study of 166 patients who randomized to receive daclatasvir, asunaprevir and 2 doses of nonnucleoside polymerase, BMS-791325 for 12 weeks.¹⁵ The overall SVR rates of 92% regardless of the non-nucleoside polymerase inhibitor dose. Thus, moving forward, the strategy will be explored with and without ribavirin in genotype 1 infected individuals. Finally, the pan genotypic NS3 protease inhibitor MK5172 was combined with the NS5a inhibitor MK 8742 with or without ribavirin. In this phase 2 study, 65 genotype 1 infected individuals received MK 5172 100 mg with ascending doses

of MK 8742 with or without ribavirin.¹⁶ Sustained response rates ranged from 89-100% and this combination will be studied in phase 3 trials moving forward.

Therapies for Hepatitis C Genotypes 2 and 3

Regarding genotype 2 and 3, the all combination of sofosbuvir and ribavirin has demonstrated high SVR rates for genotype 2 with improved SVR rates in genotype 3 infected individuals. Three large registration trials have now been completed demonstrating that for genotype 2, 12 weeks of sofosbuvir and ribavirin will lead to high sustained response rates regardless of treatment status or the presence or absence of advanced liver disease. Additional strategies are going to be required for selected genotype 3 infected individuals. The Fission study compared 12 weeks of sofosbuvir and ribavirin to 24 weeks of peginterferon and ribavirin.¹⁷ The overall SVR rates were identical at 67%. However in genotype 2 infected individuals, high sustained virologic response rates above 90% were seen in treatment naive patients regardless of the presence or absence of cirrhosis. In genotype 3 individuals without cirrhosis, 12 weeks of sofosbuvir and ribavirin led to an overall SVR rate of 61% and in cirrhotic patients, the SVR rate was just 34%. Similar patterns were seen in the Fusion nonresponder study, which evaluated 12 and 16 weeks of sofosbuvir and ribavirin. The high rates of SVR were seen in noncirrhotic patients with genotype 2 infection. In cirrhotic genotype 3 patients, increasing the duration of sofosbuvir and ribavirin from 12 to 16 weeks improved SVR rates in this nonresponder population to 61% from 19% with just 12 weeks of sofosbuvir and ribavirin. The marked improvement in SVR rates with just 4 additional weeks of sofosbuvir and ribavirin lead to an additional phase 3 European study that explored 24 weeks of sofosbuvir and ribavirin for genotype 3 infected individuals. Indeed 24 weeks of sofosbuvir and ribavirin led to an overall SVR rate in genotype 3 treatment in naive noncirrhotic patients of 94% and in treatment failures who had non-cirrhotic genotype 3 infection, 24 weeks of sofosbuvir and ribavirin led to an overall SVR rate of 87%. Treatment experienced cirrhotic patients were the only group where the SVR rates were somewhat disappointing with an overall SVR rate 60% for this genotype 3 population.¹⁸ Other strategies will be required to improve SVR rates in this group, likely the combinations of DAAs in order to achieve higher SVR rates in the advanced fibrotic genotype 3 population. As an example, 24 weeks of sofosbuvir and daclatasvir led to a SVR rate of 89% in 18 genotype 3 patients.¹⁰ Currently in United States, sofosbuvir and ribavirin is approved for genotype 2 infected individuals for 12 weeks. For genotype 3 infection, sofosbuvir and ribavirin treatment duration is for a total of 24 weeks.

CONCLUSION

In December 2013, the approval of third protease inhibitor simeprevir in combination with peginterferon and ribavirin occurred in United States and this protease in combination with peginterferon and ribavirin led to an overall SVR rate of over 80% with the majority of individuals requiring just 24 weeks of therapy. In addition, ABT-450, asunaprevir, faldaprevir, MK-5172 and other protease inhibitors will be

studied with a variety of other direct acting antiviral agents and strategies in interferon and ribavirin sparing strategies with expected SVR rates of above 90%.

Sofosbuvir in combination with peginterferon and ribavirin for 12 weeks is a new treatment paradigm with a 12 week course of therapy leading to high sustained response rates in genotype 1 and 4 infected individuals including high sustained response rates in cirrhotic patients. In addition, genotype 2 and 3 infected individuals now have an all oral regimen of sofosbuvir and ribavirin, which is highly effective in all genotype 2 infected individuals with 12 weeks of therapy. For genotype 3 infected individuals, 24 weeks of the sofosbuvir and ribavirin leads to high sustained virological response rates in most groups. However, cirrhotic genotype 3 infected individuals are going to require additional strategies to optimize SVR rates. It is expected that 2014 should see the presentation of phase 3 data with a variety of combinations of direct acting antiviral agents with the anticipated approval of these combinations occurring in late 2014 or early 2015. Moreover, one should expect that SVR rates above 90% for treatment naive and treatment failure patients should be the expected norm for all patients.

CONFLICT OF INTEREST

Paul Y. Kwo, MD, has disclosed that he has received consulting fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Novartis, and Vertex; has received fees for non-CME/CE services from Merck and has received funds for research support from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck, Roche, and Vertex.

REFERENCES

1. Centers for Disease Control and Prevention. Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965. *MMWR Recomm Rep*. 2012;61(RR-4):1-32.
2. Manns M, Marcellin P, Fred Poordad F, et al. 1413 SIMEPREVIR (TMC435) WITH Peginterferon/Ribavirin For Treatment Of Chronic Hcv Genotype-1 Infection In Treatment-Naïve Patients: Results From Quest-2, A Phase Iii Trial. *J Hepatol*. 2013;58:S568.
3. Jacobson I, Dore G, Foster G. Simeprevir (TMC435) with peginterferon/ribavirin for chronic hcv genotype 1 infection in treatment-naïve patients: results from QUEST-1, a Phase III trial. Reported in the 48th Annual Meeting of the European Association for the Study of the Liver; 2013.
4. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet*. 2013;381(9883):2100-2107.
5. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368(20):1878-1887.
6. Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of Nucleotide Polymerase Inhibitor Sofosbuvir Plus the NS5A Inhibitor Ledipasvir or the NS5B Non-Nucleoside Inhibitor GS-9669 Against HCV Genotype 1 Infection. *Gastroenterology*.
7. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide Polymerase Inhibitor Sofosbuvir plus Ribavirin for Hepatitis C. *N Engl J Med*. 2013;368(1):34-44.
8. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet*.
9. Jacobson I, Ghalib R, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Washington, DC. 2013;1-5.

10. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection. *N Engl J Med*. 2014;370(3):211-221.
11. Kowdley KV, Lawitz E, Poordad F, et al. 3 Safety And Efficacy Of Interferon-Free Regimens Of Abt-450/R, Abt-267, Abt-333 +/- Ribavirin In Patients With Chronic HCV Gt1 Infection: Results From The Aviator Study. *J Hepatol*. 2013;58:S2.
12. Chayama K, Suzuki Y, Ikeda K, et al. All-Oral Combination of Daclatasvir Plus Asunaprevir in Interferon-Ineligible Naive/Intolerant and Nonresponder Japanese Patients Chronically Infected With HCV Genotype 1b: Results From a Phase 3 Trial. 64th Annual Meeting of the American Association for the Study of Liver diseases; 2013.
13. Lawitz E, Varunok P, Thuluvath PJ, et al. Interferon- and Ribavirin-free Regimen of ABT- 450/r + ABT-267 in HCV Genotype 1b-infected Treatment-naïve Patients and Prior Null Responders. *Hepatology*. 2013;58(1):75.
14. Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and Deleobuvir for HCV Genotype 1 Infection. *N Engl J Med*. 2013;369(7):630-639.
15. Everson GT, Sims KD, Thuluvath PJ, et al. Phase 2b study of the interferon-free and ribavirin-free combination of daclatasvir, asunaprevir, and BMS-791325 for 12 weeks in treatment-naive patients with chronic HCV genotype 1 infection. 64th Annual Meeting of the American Society for the Study of Liver Diseases (AASLD). Washington, DC. 2013.
16. Lawitz E, Vierling J, Murillo A. High Efficacy and Safety of the All-Oral Combination Regimen. 2013: MK-5172/MK-8742±RBV for 12 weeks in HCV genotype 1 infected patients: the C-WORTHY study. Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases.
17. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013;368(1):34-44.
18. Zeuzem S, Dusheiko G, Riina Salupere R. Sofosbuvir+ ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE Trial. 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013. 1-5.