Update on hepatitis C: Direct-acting antivirals

Leon L Seifert, Ryan B Perumpail, Aijaz Ahmed

Leon L Seifert, Department of Transplantation Medicine, University Hospital Münster, 48149 Münster, Germany

Ryan B Perumpail, Aijaz Ahmed, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA 94305, United States

Author contributions: Seifert LL, Perumpail RB and Ahmed A designed research and analyzed data; Seifert LL performed research and wrote the paper.

Conflict-of-interest statement: We declare that we have no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Aijaz Ahmed, MD, Associate Professor of Medicine, Medical Director Liver Transplant Program, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 750 Welch Road, Suite 210, Stanford, CA 94305, United States. aijazahmed@stanford.edu
Telephone: +1-650-4986091
Fax: +1-650-4985692

Received: July 20, 2015
Peer-review started: July 24, 2015
First decision: October 22, 2015
Revised: October 24, 2015
Accepted: November 23, 2015
Article in press: November 25, 2015
Published online: December 8, 2015

Abstract
Hepatitis C virus (HCV) was discovered 26 years ago. For decades, interferon-based therapy has been the mainstay of treatment for HCV. Recently, several direct-acting antivirals (DAAs) have been approved for treatment of HCV-infected patients and to help combat the virus. These drugs have revolutionized the management of HCV as all-oral regimens with favorable side effect profiles and superior rates of sustained virological response. Emerging real-world data are demonstrating results comparable to registration trials for DAA agents. Suddenly, the potential for eradicating HCV is on the horizon.

Key words: Hepatitis C virus; Direct-acting antivirals; Sustained virologic response; Management; Treatment

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Recently, several direct-acting antivirals (DAAs) have been approved for treatment of hepatitis C virus (HCV)-infected patients and to help combat the virus. These drugs have revolutionized the management of HCV as all-oral regimens with favorable side effect profiles and superior rates of sustained virological response. Emerging real-world data are demonstrating results comparable to registration trials for DAA agents. Suddenly, the potential for eradicating HCV is on the horizon.

Seifert LL, Perumpail RB, Ahmed A. Update on hepatitis C: Direct-acting antivirals. World J Hepatol 2015; 7(28): 2829-2833 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i28/2829.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i28.2829

INTRODUCTION
Hepatitis C virus (HCV) was discovered 26 years ago in 1989, previously the HCV-related clinical entity was referred to as non-A, non-B hepatitis[1]. Currently, HCV has created a major health burden, with approximately 180 million infected people worldwide, representing about 2%-3% of the world’s population[2]. This single-stranded, positive-sense 9.6 kb RNA-virus is globally
Seifert LL et al. An update on hepatitis C

prevalent, showing geographic variation in its genotypic distribution and represents a major cause of end-stage liver disease\[6,7\]. About 4 out of 5 patients acutely infected with HCV develop a chronic hepatitis while only 20% of patients demonstrate spontaneous recovery with eradication of HCV\[5\]. Chronic hepatitis C (CHC) is a leading cause of cirrhosis and is complicated by development of hepatocellular carcinoma in 1%-4% of cirrhotic patients\[6,7\].

Until recently, interferon (IFN)-based therapies represented the mainstay of treatment for HCV infection. Modifications of the treatment-regimens including pegylation of IFN and the addition of ribavirin (RBV) resulted in suboptimal improvement sustained virologic response (SVR) and an unfavourable adverse effects profile. Based on the HCV genotype (GT) and the treatment-experience, only 40% to 70% of patients achieved SVR, with poorer outcomes among people infected with the more prevalent GT1\[8\]. The approval of the first-generation direct acting antiviral (DAA) agents, telaprevir (TLV) and boceprevir (BCV), in 2011 provided improvement in SVR for the targeted HCV GT1\[9\]. Unfortunately, TLV and BCV therapy was complicated by cumbersome schema of drug intake and the broad range of adverse events.

With the release of sofosbuvir in 2013 and 2014 in most Western countries, a new era in the treatment of CHC began. An all-oral, IFN-free antiviral treatment for CHC with DAA agents became available for the first time. In addition to sofosbuvir, approvals of other second-generation DAA agents, which target different proteins of HCV have improved the efficacy of antiviral therapy with better tolerance. The superior SVR rates from several phase III trials have recently been confirmed by a number of real-life experience reports. We review various DAA-based antiviral regimens for HCV-infected patients.

MOLECULAR STRUCTURE OF HCV - TARGET SITES FOR DAA AGENTS

HCV is a member of the Flaviviridae virus family\[10-12\]. Its RNA is single-stranded and positive-sensed with a size of approximately 9.6 kb. The precursor-polyprotein is post-translationally processed and modified by a cooperation of cellular and viral proteases\[13,14\]. Bench mark molecular biology research on HCV has led to a better understanding of its replication cycle and has been instrumental in the discovery and development of molecules blocking viral proteins, specifically the DAA's\[15-17\]. The HCV-genome encodes for 9 proteins - 2 are structural (E1 and E2) and 7 non-structural (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B)\[10,11,13,14\]. These proteins provide targets for the DAA's, being mostly essential in the virus cycle of replication\[10-14\]. NS5B is a polymerase and a prime target for antiviral agents\[18,19\]. Antiviral agents are classified as inhibitors of nucleoside-type and non-nucleoside type. The active site of NS5B is highly conserved compared to other parts of the HCV-genome\[18,19\]. Currently, sofosbuvir is the only clinically available NS5B-inhibitor (nucleoside-type) with pan-genotypic antiviral activity and higher barrier to resistance compared to other DAA's\[18,19\]. It is a pro-drug and currently represents the backbone of most treatment-regimens\[20,21\]. Inhibition of the NS3/4A protease-complex is another potential target for DAA's. The first-generation DAA's, TLV and BCV were inhibitors of NS3/4A, and referred to as protease-inhibitors. Currently, two NS3/4A-inhibitors are approved in the United States and the European Union - paritaprevir, which is approved for the treatment of HCV GT1 in combination with ombitasvir and dasabuvir; and simeprevir, which is approved in combination with sofosbuvir for GT1 patients. DAA's targeting NS5A have also been approved\[22-25\]. Currently, three different NS5A-Inhibitors are approved in the United States and/or the European Union - daclatasvir, which is given in combination with sofosbuvir ± RBV for the treatment of the GTs 1-4; ombitasvir (ABT-267), which is approved for the treatment of GT1 in combination with paritaprevir and dasabuvir; and ledipasvir, which is approved for GT1, 3 and 4 in combination with sofosbuvir ± RBV.

DAA AGENTS - REGIMEN BASED ON HCV GT

With the approval of sofosbuvir in December of 2013 in North America (United States and Canada) and in January 2014 in Europe, an all-oral antiviral treatment for CHC with DAA's was available for the first time. In 2014, several studies analyzing the efficacy and the impact of the DAA-based therapies have been published. The response rates have been reproduced in real-life experiences (TRIO and TARGET 2.0) as welf\[26-29\].

HCV GT1 is the most common GT with an overall prevalence of 46.2%. In particular, GT1 is more prevalent in the Western countries of North America and Western Europe (75.8% and 59.0% respectively). Accordingly, most studies have focused on the treatment of GT1. Patients with GT2 and GT3 are less prevalent worldwide (GT2 9.1% and GT3 30.1%) with a noticeable variation in distribution within Western countries - North America (GT2 12.0% and GT3 10.4%) and Western Europe (GT2 10.8% and GT3 24.8%). Patient with GT 4, 5 and 6 demonstrate the lowest prevalence (GT4 8.3%, GT5 0.8%, and GT6 5.4%) worldwide, with highest prevalence in low-income countries, and limited data on experience with second-generation DAA's\[4\].

In phase-3 SAPPHIRE-I clinical trial the combination of ritonavir-boosted ABT-450/r (protease inhibitor)-ombitasvir (NS5A inhibitor), and dasabuvir (non-nucleoside NS5B) with RBV were studied in treatment-naive, non-cirrhotic HCV-infected non-cirrhotic patients with GT1. RBV was added according to body weight (≥ 75 kg 1200 mg/d or < 75 kg 1000 mg/d). Overall, 96.2% of patients achieved SVR (GT1b 98.0% and GT1a 95.3%). A higher stage of fibrosis and obesity were the negative predictive factors with SVR-12 rates still > 90% and thus satisfactory\[30\]. Treatment-experienced patients were studied in the SAPPHIRE-II clinical trial.
Table 1 Direct-acting antiviral-based regimens for treatment-naive hepatitis C virus-infected patients

| Genotype | Recommended regimens options |
|----------|-----------------------------|
| GT1a     | SOF/LDV × 12 wk              |
|          | P;OD + RBV × 12 wk (no cirrhosis) - 24 wk (cirrhosis) |
|          | SOF + SMV + RBV × 12 wk (no cirrhosis) - 24 wk (cirrhosis without Q80K variant) |
|          | SOF + DCV × 12 wk (no cirrhosis) - 24 wk (cirrhosis ± RBV) |
| GT1b     | SOF/LDV × 12 wk              |
|          | P;OD + RBV × 12 wk (no cirrhosis) |
|          | SOF + SMV + RBV × 12 wk (no cirrhosis) - 24 wk (cirrhosis) |
|          | SOF + DCV × 12 wk (no cirrhosis) - 24 wk (cirrhosis ± RBV) |
| GT2      | SOF + RBV × 12 wk (no cirrhosis) - 16 wk (cirrhosis) |
|          | SOF + DCV × 12 wk (RBV intolerant) |
| GT3      | SOF + PegIFN + RBV × 12 wk (PegIFN eligible) |
|          | SOF + DCV × 12 wk (no cirrhosis) - 24 wk (cirrhosis ± RBV) |
|          | SOF + RBV × 24 wk (PegIFN ineligible) |
| GT4      | SOF/LDV × 12 wk              |
|          | P;OD + RBV × 12 wk           |
|          | SOF + RBV × 24 wk            |
|          | SOF + PegIFN + RBV × 12 wk   |
|          | SOF + SMV + RBV × 12 wk      |
| GT5      | SOF/LDV × 12 wk              |
|          | SOF + PegIFN + RBV × 12 wk   |
| GT6      | SOF + PegIFN + RBV × 12 wk   |
|          | SOF + PegIFN + RBV × 12 wk   |
|          | SOF/LDV × 12 wk              |
|          | SOF + PegIFN + RBV × 12 wk   |

GT: Genotype; SOF: Sofosbuvir; LDV: Ledipasvir; PrOD: Paritaprevir + ritonavir + ombitasvir + dasabuvir; RBV: Ribavirin; SMV: Simeprevir; DCV: Daclatasvir; PegIFN: Pegylated interferon.

Again, a high grade of fibrosis and obesity were negative predictive factors, with an overall SVR-12 of 96.3% (GT1a 96% and GT1b 96.7%)\(^{[33]}\).

The ION clinical trials (ION-I, ION-II and ION-III) examined the efficacy of sofosbuvir and ledipasvir co-formulation with and without RBV for 12 to 24 wk in treatment-naive (16% with cirrhosis) HCV-infected GT1 patients\(^{[31]}\). SVR-12 was 97%-99% in ION-I clinical trial. There was no statistically significant difference between the duration of the treatment (12 wk vs 24 wk), HCV sub-GT (GT1a vs GT1b) or RBV use. Even the presence of cirrhosis did not impact the SVR\(^{[32,33]}\). Treatment-experienced HCV-infected GT1. Patients were treated with sofosbuvir and ledipasvir co-formulation ± RBV for 12 or 24 wk in ION-II clinical trial. In these patients, addition of RBV did not impact the SVR. Previously treated patients with cirrhosis were the only sub-group that demonstrated a higher SVR with 24 wk of therapy. Therefore, 24 wk of treatment was recommended for previously treated patients with cirrhosis\(^{[34]}\). In the ION-III clinical trial, the possibility of shortening the treatment to 8 wk in previously untreated patients without cirrhosis was evaluated. A high number of patients reached SVR in all groups (93% to 95%) without a significant impact of the duration of the treatment or the addition of RBV in the 8-wk treatment\(^{[35]}\). Based on secondary analysis, patients with baseline HCV RNA level greater than 6 million international units per milliliter demonstrated a higher risk of relapse with 8 wk of therapy. Therefore, 8 wk of therapy is recommended for treatment-naive, non-cirrhotic HCV-infected patients with pre-treatment HCV RNA viral load of less than 6 million international units per milliliter\(^{[36]}\).

In the COSMOS trial, the SVR to sofosbuvir and simeprevir combination in previous non-responders with METAVIR scores between F0 and F2 was compared to previous non-responders and treatment-naive patients with METAVIR scores between F3 and F4. The SVR-12 rates were similar in both groups, showing 90% SVR-12 in patients with METAVIR scores F0-F2 and 94% SVR-12 in patients with METAVIR score F3-F4. Neither the duration of the treatment (12 wk vs 24 wk) nor the addition of RBV seemed to influence the SVR\(^{[36]}\).

The combination of sofosbuvir and daclatasvir DCV has been safe and effective, both, in previously treated and untreated HCV-patients with GT\(^{[37,38]}\). In previously untreated HCV-infected GT1 patients, a SVR-12 of 98% was achieved with no significant impact of the duration of the treatment (12 wk vs 24 wk) or the addition of RBV\(^{[37]}\). In previously treated patients, 24 wk of treatment with sofosbuvir and daclatasvir demonstrated a SVR-12 of 97.5% with no influence from RBV addition\(^{[37]}\).

Please refer to Tables 1 (treatment-naive) and 2 (treatment-experienced) for treatment recommendation by HCV GT with DAA agents\(^{[38-44]}\).

**CONCLUSION**

The current developments in the treatment of CHC are extraordinary. A significant improvement in efficacy
provided by the DAA agents has been long awaited. In addition to higher efficacy, DAA agents are tolerable with favorable adverse effects profile. Improved efficacy combined with easy tolerability is welcome news for a wide spectrum of patients who were not able to pursue interferon-based antiviral therapy for CHC. Impediments to DAA-based therapy include the high cost of therapy. Efforts are underway to make DAA agents affordable in Asia and Africa. Other issues include a cumbersome insurance authorization process in the United States. It is important to educate the patients that HCV treatment with DAA agents does not confer immunity and exposure to risk factors can lead to re-infection.

REFERENCES

1 Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244: 359-362 [PMID: 2523562 DOI: 10.1126/science.2523562]

2 Mohd Hanafiah F, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013; 57: 1333-1342 [PMID: 23172780 DOI: 10.1002/hep.26141]

3 Halliday J, Klenerman P, Barnes E. Vaccination for hepatitis C virus: closing in on an evasive target. Expert Rev Vaccines 2011; 10: 659-672 [PMID: 21604986 DOI: 10.1586/erv.11.55]

4 Messina JP, Humphreys I, Flaxman AD, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015; 61: 77-87 [PMID: 25069599 DOI: 10.1002/hep.27259]

5 Marcellin P. Hepatitis C: the clinical spectrum of the disease. J Hepatol 1999; 31 Suppl 1: 9-16 [PMID: 10622254 DOI: 10.1016/S0168-8278(99)80368-7]

6 Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001; 345: 41-52 [PMID: 11439948 DOI: 10.1056/NEJM200010735430107]

7 Zoulim F, Chevallier M, Maynard M, Trepo C. Clinical consequences of hepatitis C virus infection. Rev Med Virol 2003; 13: 57-68 [PMID: 12156062 DOI: 10.1002/rmv.371]

8 Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Penn CY, Chang TT, Everson GT, Hoo J, Gieken G, Yoffe B, Towner WJ, Bourliere M, Metivier S, Chu CJ, Sievert W, Brownwick JP, Thabet D, Lee YJ, Kao JH, McPhee F, Kopit J, Mendez P, Linaberry M, Hughes G, Noviello S. All-oral daclatasvir plus asunaprevir for the treatment of chronic hepatitis C virus infection with favorable adverse effects profile. Improved efficacy and tolerability. J Gastroenterol Hepatol 2014; 29: 478-487 [PMID: 24387618 DOI: 10.1111/ajh.12601]

9 Appel N, Schaller T, Penin F, Bardenschaffer R. From structure to function: new insights into hepatitis C virus RNA replication. J Biol Chem 2006; 281: 9833-9836 [PMID: 16407182 DOI: 10.1074/jbc.R500026200]

10 He Y, Staschke KA, Tan SL. HCV NS5A: a multifunctional regulator of cellular pathways and viral replication. In Hepatitis C Viruses. In: Tan SL, editor. SourceHepatitis C Viruses: Genomes and Molecular Biology. Norfolk (UK): Horizon Bioscience, 2006: Chapter 9 [PMID: 21250384]

11 Szabo G. Hepatitis C virus NS5A protein—a master regulator? Gastroenterology 2006: 130: 995-999 [PMID: 16530536 DOI: 10.1053/j.gastro.2006.01.072]

12 Huang Y, Staschke K, De Francesco R, Tan SL. Phosphorylation of hepatitis C virus NS5A nonstructural protein: a new paradigm for phosphorylation-dependent viral RNA replication? Virology 2007; 364: 1-9 [PMID: 17400273 DOI: 10.1016/j.virol.2007.01.042]

13 Backus LI, Belperio PS, Shahouman TA, Loomis PT, Mole LA. Effectiveness of sofosbuvir-based regimens in genotype 1 and 2 hepatitis C virus infection in 4026 U.S. Veterans. Aliment Pharmacol Ther 2014; 42: 559-573 [PMID: 26113432 DOI: 10.1111/apt.13300]

14 Höner Zu Siederdissen C, Maasoumy B, Dextering K, Port K, Sollik L, Mix C, Kirschner J, Cornberg J, Mann MPP, Wodenehb H, Cornberg M. Eligibility and safety of the first interferon-free therapy against hepatitis C in a real-world setting. Liver Int 2015; 35: 1845-1852 [PMID: 25556625 DOI: 10.1111/liv.12774]

15 Dieterich D, Bacon BR, Flamm SL, Kowdle KV, Milligan S, Tsai N, Younossi ZM, Lawitz E. Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network: academic and community treatment of a real-world, heterogeneous population. 65th Annual Meeting of the American Association for the Study of
Liver diseases. Boston, USA, 2014: Abstract 46

29 Jensen DM, O’Leary JG, Pockros PJ, Sherman KE, Kwo PY, Mailliard ME, Kowdley KV, Muir AJ, Dickson RC, Ramani A, Manns MP, Lok AS, Akushevich L, Nelson DR, Fried MW. Safety and efficacy of sofosbuvir-containing regimens for hepatitis C: real-world experience in a diverse, longitudinal observational cohort. 65th Annual Meeting of the American Association for the Study of Liver diseases. Boston, USA, 2015: Abstract 45

30 Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, Weiland O, Aguilar H, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; 370: 1594-1603 [PMID: 24720703 DOI: 10.1056/NEJMoa1315722]

31 Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poorfard D, Bourlière M, Sulkowski MS, Wedemeyer H, Tam E, Desmond P, Jensen DM, Di Biscaglie AM, Varunok P, Hassanein T, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; 370: 1604-1614 [PMID: 24720679 DOI: 10.1056/NEJMoa1410156]

32 Younossi ZM, Stepanova M, Marcellin P, Afghal N, Kowdley KV, Zeuzem S, Hunt SL. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: Results from the ION-1, -2, and -3 clinical trials. *Hepatology* 2015; 61: 1798-1808 [PMID: 25627448 DOI: 10.1002/hep.27724]

33 Afghal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herrin R, Lalezari J, Younes ZH, Pockros PJ, Di Biscaglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; 370: 1483-1493 [PMID: 24725238]

34 Afghal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Brâu N, Buti M, Jacobson JM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for chronic genotype 1 HCV infection. *N Engl J Med* 2014; 370: 1889-1898 [PMID: 24725239]

35 Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, Schiff E, Ghalib R, Ryan M, Rustgi V, Chojkier M, Herrin R, Di Biscaglie AM, Pockros PJ, Subramanian GM, An D, Svarovskaia E, Hyland RH, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Pound D, Fried MW. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014; 370: 1879-1888 [PMID: 24720702 DOI: 10.1056/NEJMoa1402355]

36 Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, Pearlman B, Rabinvobin M, Gitlin N, Lim JK, Pockros PJ, Scott JD, Fievery B, Lambrecht T, Ouwerkerk-Mahadevan S, Callewaert K, Symonds WT, Picchio G, Lindsay KL, Beaumont M, Jacobson IM. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet* 2014; 384: 1756-1765 [PMID: 25078309]

37 Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanin T, Jacobson I, Lawitz E, Lok AS, Hinerestosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquenni C, Grassela DM. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; 370: 211-221 [PMID: 24428467 DOI: 10.1056/NEJMoa1306218]

38 Kumada H, Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, Kawakami Y, Ido A, Yamamoto K, Takaguchi K, Izumi N, Koike K, Takehara T, Kawada N, Sato M, Miyagoshi H, Eley T, McPhee F, Damokosh A, Ishikawa H, Hughes E. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. *Hepatology* 2014; 59: 2083-2091 [PMID: 24604476 DOI: 10.1002/hep.27113]

39 Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Weiland O, Reesink HW, Ferenci P, Hézode C, Esteban R. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; 370: 1993-2001 [PMID: 24795201 DOI: 10.1056/NEJMoa1316145]

40 Omata M, Nishiguchi S, Ueno Y, Mochizuki H, Izumi N, Ikeda F, Toyoda H, Yokosuka O, Nirei K, Genda T, Umemura T, Takehara T, Sakamoto N, Nishigaki Y, Nakane K, Toda N, Ide T, Yanase M, Hino K, Gao B, Garrison KL, Dvory-Sobol H, Ishizaki A, Onmote M, Brainard D, Knox S, Symonds WT, McHutchison JG, Yatsushahi H, Mizokami M. Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. *J Viral Hepat* 2014; 21: 762-768 [PMID: 25196837 DOI: 10.1111/jvhe.12312]

41 Gane EJ, Hyland RH, An D, Pang PS, Symonds WT, McHutchison JG, Stedman CA. Sofosbuvir/ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated genotype-1 patients, and genotype-1 patients with prior sofosbuvir treatment experience. *J Hepatol* 2014; 60: S1-S22 [DOI: 10.1016/S0168-8278(14)60008-8]

42 Ruane PJ, Ain D, Meshrekey R, Riad J, Stryker R, Soliman M, Mikhail S, Wolfe PR, Kersey K, Doehle B, Deyuan J, Symonds WT. Sofosbuvir plus ribavirin, an interferon-free regimen, in the treatment of treatment-naive and treatment-experienced patients with chronic genotype 4 HCV infection. *J Hepatol* 2014; 60: S503-S504 [DOI: 10.1016/S0168-8278(14)60363-3]

43 AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD/IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015; 62: 932-954 [PMID: 26111063 DOI: 10.1002/hep.27950]

44 European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015; 63: 199-236 [PMID: 25911336 DOI: 10.1016/j.jhep.2015.03.025]

P- Reviewer: Chiu KW, Kanda T, Malnick SDH, Panduro A
S- Editor: Ji FF
L- Editor: A
E- Editor: Liu SQ
