EDITORIAL

Korean J Intern Med 2023;38:454-455
https://doi.org/10.3904/kjim.2023.248

Sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir: novel treatment options for naïve and previously treated hepatitis C infection

Hyun Phil Shin

Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Seoul, Korea

See Article on Page 504-513

Long-term chronic hepatitis C virus (HCV) infection causes liver fibrosis that can lead to cirrhosis, hepatic decompensation, and hepatocellular carcinoma. Therefore, eradicating HCV infection has numerous health benefits [1]. In 2016, the World Health Organization set a goal to eliminate hepatitis C by 2030 [2], but many countries are progressing at different paces, depending on their screening strategies and access to treatment. The goal of HCV treatment is to cure the infection by achieving a sustained virological response (SVR), defined as undetectable HCV RNA after completing treatment. The development of treatment regimens that interfere with HCV replication directly could lead to a cure [3]. The treatment outcomes of patients with chronic HCV infection have substantially evolved since the introduction of direct-acting antiviral agents (DAAs), because DAAs are generally well tolerated, safe, and more effective than interferon-based treatment [1].

HCV genotyping is not required for treatment-naive patients without cirrhosis if a pangenotypic regimen is used. Considering their virological efficacy, ease of use, and safety, pangenotypic DAA-based regimens are preferred in HCV treatment for treatment-naïve and treatment-experienced patients. Sofosbuvir–velpatasvir, glecaprevir–pibrentasvir, and sofosbuvir–velpatasvir–voxilaprevir are the currently recommended pangenotypic DAAs for patients without cirrhosis or with compensated cirrhosis [4].

Glecaprevir (100 mg) and pibrentasvir (40 mg) are available in a two-drug fixed dose combination and prescribed as three tablets once daily with food, as glecaprevir increases 83–163% in plasma after eating [4]. The efficacy and safety of glecaprevir (NS3-4A protease inhibitor)–pibrentasvir (NS5A inhibitor) have been investigated in a clinical trial. The SVR rates were 94% in intention-to-treat and 99.3% in per protocol analysis, irrespective of fibrosis stage, baseline HCV-RNA, or chronic kidney disease stage [5]. However, DAA regimens containing a protease inhibitor such as grazoprevir, glecaprevir, or voxilaprevir are contraindicated in patients with decompensated cirrhosis because of higher protease inhibitor concentrations and related toxicity [6]. Concomitant administration with glecaprevir–pibrentasvir and organic anion-transporting polypeptide 1B1/3 may increase the concentrations of the substrates of organic anion-transporting polypeptide 1B1/3, and the lipid-lowering agents atorvastatin and simvastatin are contraindicated for this reason [4].

Sofosbuvir (400 mg) and velpatasvir (100 mg) are available in a two-drug fixed-dose combination in a single tablet. Velpatasvir levels in plasmas are similar in patients with decompensated cirrhosis (Child–Pugh B and C cirrhosis) compared to those with normal hepatic function [4]. In the ASTRAL-4 study, the combination of sofosbuvir (NS5B polymerase inhibitor) and velpatasvir (NS5A inhibitor) with or without ribavirin was used for a wide spectrum of patients, including those with decompensated cirrhosis (Child–Pugh B or C) or prior episodes of decompensation [7].

Sofosbuvir (400 mg), velpatasvir (100 mg), and voxilaprevir (100 mg) are available in a three-drug fixed-dose combination in a single tablet. The POLARIS-1 and POLARIS-4 phase III trials reported the safety and efficacy of this triple combination for 12 weeks in patients who failed to achieve SVR after a DAA-based regimen, including patients exposed

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

to protease or NS5A inhibitors [8]. Compared to patients with normal liver function, the voxilaprevir AUC was 3- and 5-fold higher in patients with moderate (Child–Pugh B) and severe (Child–Pugh C) hepatic impairment, respectively. Therefore, it should not be used in patients with decompensated cirrhosis [4].

Few prospective clinal trials have examined sofosbuvir–velpatasvir or sofosbuvir–velpatasvir–voxilaprevir In Asia, including Korea. Heo et al. were the first to report the efficacy and safety of these two regimens for naïve and previously treated hepatitis C infection in Korea [9]. In that study, SVR12 was achieved in 98% (52/53) of the participants who received sofosbuvir–velpatasvir and 100% (33/33) of the sofosbuvir–velpatasvir–voxilaprevir treatment group. No participants had serious drug-related adverse events. One participant in the sofosbuvir–velpatasvir group discontinued treatment and experienced virologic relapse. Sofosbuvir–velpatasvir does not contain an NS3-4A protease inhibitor and can be used in decompensated patients, while patients with decompensated cirrhosis were not included in that study. Daclatasvir (NS5A inhibitor)–asunaprevir (NS3-4A protease inhibitor) combination therapy was widely used with relatively good efficacy when DAAs were introduced in Korea, but options for treatment failure after regimens containing an NS5A inhibitor included were limited. Their study is important clinically because the SVR12 rate for the sofosbuvir–velpatasvir–voxilaprevir group was 100%, and it even included NS5A inhibitor-experienced patients [9].

In conclusion, the sofosbuvir–velpatasvir regimen has expanded indications and options with good efficacy. Sofosbuvir–velpatasvir–voxilaprevir treatment is an alternative for patients who fail on existing treatments. A large-scale prospective study that includes all genotypes and patients with decompensated cirrhosis would help to define its real-world efficacy and safety under various situations.

REFERENCES

1. Ghany MG, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology 2020;71:686-721.
2. World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. Geneva: World Health Organization, 2016: 1-56.
3. Liang TJ, Feld JJ, Cox AL, Rice CM. Controlled human infection model - fast track to HCV vaccine? N Engl J Med 2021;385:1235-1240.
4. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; Clinical Practice Guidelines Panel: Chair:; EASL Governing Board representative:; Panel members:. EASL recommendations on treatment of hepatitis C: Final update of the series☆. J Hepatol 2020;73:1170-1218.
5. D'Ambrosio R, Pasulo L, Puoti M, et al.; NAVIGATORE-Lombardia Study Group. Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C. J Hepatol 2019;70:379-387.
6. U. S. Food and Drug Administration. FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease [Internet]. Silver Spring (MD): FDA [cited 2023 Jun 1]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-.
7. Curry MP, O'Leary JG, Bzowej N, et al.; ASTRAL-4 Investigators. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618-2628.
8. Bourlière M, Gordon SC, Flamm SL, et al.; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med 2017;376:2134-2146.
9. Heo J, Kim YJ, Lee SW, et al. Efficacy and safety of sofosbuvir–velpatasvir and sofosbuvir–velpatasvir–voxilaprevir for hepatitis C in Korea: a Phase 3b study. Korean J Intern Med 2023;38:504-513.

Received : June 5, 2023
Accepted : June 14, 2023

Correspondence to
Hyun Phil Shin, M.D., Ph.D.
Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea
Tel: +82-2-440-6115, Fax: +82-2-440-7849
E-mail: drshp@khu.ac.kr
https://orcid.org/0000-0002-9350-1079

Conflicts of interest
The author discloses no conflicts.

Funding
None