Recent update of the 2017 Korean Association for the Study of the Liver (KASL) treatment guidelines of chronic hepatitis C: Comparison of guidelines from other continents, 2017 AASLD/IDSA and 2016 EASL

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The paradigm for the treatment of chronic hepatitis C (CHC) has been changed due to the development of direct acting antivirals (DAAs) of hepatitis C virus (HCV). The high sustained virologic response rate and ease of administration makes the DAAs approach ideal to contribute to the complete eradication of HCV. Currently, treatment options for individual patients vary depending on the genotype or subtype of HCV, presence or absence of liver cirrhosis, previous experience of antiviral treatment or resistance associated substitutions. Because of drug availability, cost-effectiveness, preference, compliance and greater possibility of desirable effects and presumed patient-important outcomes may vary between countries, treatment options for individual patients are different. The review focuses on the comparing the current treatment options for CHC in other continents with the 2017 Korea Association for the Study of the Liver guidelines. (Clin Mol Hepatol 2018;24:278-293)

Keywords: Hepatitis C virus; Direct acting antiviral; Resistance associated substitutions; Genotype; Liver cirrhosis

INTRODUCTION

Since the development of direct acting antivirals (DAAs) against hepatitis C virus (HCV), the paradigm for the pharmacological management of chronic hepatitis C has been changed. The ease of administration and high sustained virologic response rate (SVR) makes...
the DAA approach ideal to contribute to the complete eradication of HCV.

Currently, treatment options for an individual patient vary depending on the genotype (GT), subtype, previous treatment experience, presence or absence of liver cirrhosis (LC) or resistance associated substitutions (RASs). Also, re-treatment options for the patients who failed previous DAA therapy are limited. Since the development of the first generation DAA, there has been much progress, including the introduction of pan-genotypic new DAA, DAA which have activity against HCV with RASs, and the publication of many novel research results from both Korea and other countries.

In Korea, the guidelines regarding “chronic hepatitis C (CHC)” were first developed in 2004 and revised in 20131, 20152, and 20173 by the Korea Association for the Study of the Liver (KASL). The HCV guidance by the American Association for the Study of Liver Disease (AASLD) and the Infectious Disease Society of America (IDSA) was recently released in September 20174. The European Association for the Study of the Liver (EASL) recommendation on treatment of hepatitis C 20165 is expected to be revised soon. Because drug availability, greater possibility of desirable effects, cost-effectiveness, preference, and compliance and presumed patient-important outcomes may vary between countries, treatment options for individual patients are different. In this article, I intended to compare the treatment options for CHC in other continents with the 2017 KASL guidelines.

CURRENTLY AVAILABLE DAA\textsc{s} IN KOREA, YEAR 2017

In Korea, the currently available DAA are ledipasvir/sofosbuvir (LED/SOF), sofosbuvir (SOF), daclatavir (DCV), asunaprevir (ASV), ombitasvir/paritaprevir/ritonavir (OPr), dasabuvir(D) and elbasvir/grazoprevir (EBR/GZR). Sofosbuvir/velpatasvir (SOF/VEL), Glecaprevir/pibrentasvir (G/P) and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) are not available yet. Simeprevir (SIM) is not available in Korea.

In Korea, the criteria for payment under the medical care benefits are as follows: for GT1b patients with treatment-naïve (TN) and treatment-experienced (TE) CHC and compensated cirrhosis (CC), OPr+D, EBR/GZR (add R if protease inhibitor [PI]+PR fail), and DCV+ASV; for GT1b patients who are RAS positive or for those who are not qualified for DCV+ASV (including decompensated LC (DC), post-liver transplantation [LT], or side effects), LED/SOF or DCV+SOF; for GT1a patients, LED/SOF, OPr+D+ribavirin (R), EBR/GZR (±R), DCV+SOF, SOF+PR; for GT1 post-LT patients with fibrosis less than F2, OPr+D+R; for DC or post-LT GT1 patients, LED/SOF+R or DCV+SOF+R; for GT2 patients, SOF+R; for GT3 patients, DCV+SOF (±R); for GT4 patients, OPr+R, EBR/GZR (±R), SOF+PR or SOF+R. Treatment duration and combination with or without ribavirin may differ from individual patients with each GT. Besides DAA, it is possible to prescribe PEG-interferon alpha. Currently available DAA and the drugs covered for payment under the medical care benefits for each GT are listed in Table 1.

NEW DAA\textsc{s}, YEAR 2017

Differently from the 2015 KASL guidelines, which introduced DAA including LED/SOF, SOF, DCV, ASV, OPr+D, SOF+PR and SIM, the 2017 KASL guidelines included new DAA, such as EBR/GZR, SOF/VEL, G/P and SOF/VEL/VOX. The results from clinical studies for new DAA will be described briefly.

EBR/GZR

According to the 2017 KASL guidelines, EBR/GZR is recommended for GT1 and GT4 patients, respectively. In a phase 3 study of TN CHC patients including GT1b, GT1a, GT4, and GT6 treated with EBR/GZR showed an SVR of 99%, 92%, 100%, and 80%, respectively.6 NSSA RASs were detected in 12% of GT1a patients, and the SVR was significantly lower in patients with RASs compared to those without RASs (58% vs. 99%). A pooled analysis of phase 2 and 3 clinical trials revealed that the SVR was 100% in GT1a infected patients with baseline NSSA RASs treated with EBR/GZR and ribavirin for 16 or 18 wk.7

G/P

A phase 3 study that assessed the efficacy and safety of 8- or 12-wk G/P treatment in HCV GT1 patients without LC (n=703, IFN-based TE patients 28%, SOF-based TE patients 0.4%) showed an SVR of 99% and 99.7%, respectively.8 A pooled analysis of phase 2 or 3 study in patients with GT1-6 chronic HCV infection without cirrhosis (interferon-based TE patients 23%, SOF-based TE patients 1%) treated with G/P for 8 or 12 wk, showed the following SVR in 8 vs. 12 wk: GT1 (100% vs. 100%), GT2 (99% vs. 100%), GT3 (97% vs. 98%), GT4 (100% vs. 100%), GT5 (100% vs. 100%), and GT6 (100% vs. 100%).9 A phase 3 study among HCV GT1, 2, 4, 5, 6 infected patients with CC (n=146, IFN-based TE 17%, SOF-based TE 8%) treated with G/P for 12 wk showed SVR of 99%, 100%, 100%, 100%,
100%, respectively. In a phase 2 study regarding G/P treatment for 12 or 16 wk in GT3 patients without LC and G/P treatment for 16 wk in TE GT3 patients with LC (PR experienced patients 54%, SOF+R±PEG-IFN experienced patients 46%), SVR were 91%, 96%, respectively. The results of clinical trials for G/P in patients who failed DAA treatment will be described in each section.

**SOF/VEL**

In a phase 3, double-blind, placebo-controlled study among untreated and previously treated HCV GT1b, GT1a, GT2, GT4, GT5, or GT6 infected patients (LC 19%, TE 32%), the SVR of SOF/VEL treatment for 12wk were 99%, 98%, 100%, 100%, 97%, and respectively. In a phase 3 study comparing a 12 wk SOF/VEL therapy to a 12wk SOF+R therapy in GT3 patients (LC 29%, TE 26%), the SVR were 95% and 80%, respectively. The prevalence of RAS in GT3 patients treated with SOF/VEL was 16%. In patients with or without NS5A RAS, the SVR were 88% and 97%, respectively. In TN GT3 patients treated with SOF/VEL, SVR noncirrhotic and cirrhotic patients were 98% and 93%, respectively. In TE patients, SOF/VEL treatment for 12wk in noncirrhotic and cirrhotic patients resulted in a SVR of 91% and 89%, respectively.

**SOF/VEL/VOX**

In a phase 3, open-label trial, HCV infected GT1-6 patients, who

| Direct acting antivirals (DAA) | KMFD approved* | Drugs covered for payment under the medical care benefit** | 2017 KASL guideline*** |
|-------------------------------|----------------|---------------------------------------------------------------|------------------------|
| Ledipasvir/sofosbuvir (LED/SOF) | Yes | GT1a, GT1b with RAS, decompensated LC, post-LT | GT1b, GT1a, GT4, GT5, GT6 |
| Sofosbuvir (SOF) | Yes | Combined with ribavirin, PR or DCV | Refer to below |
| Daclatasvir (DCV) | Yes | DCV+ASV in GT1b, DCV+SOF in GT3, DCV+ASV in GT1a, GT1b with RAS, GT1 with decomp. LC, post LT | DCV+ASV in GT1b, DCV+SOF in GT1-GT6, DCV+ASV in decompensated LC & post-LT |
| Aunaprevir (ASV) | Yes | DCV+ASV in GT1b | DCV+ASV in GT1b |
| Ombitasvir/paritaprevir/ritonavir (OPr) | Yes | OPrD in GT1, OPr in GT4 | OPrD in GT1, OPr in GT4 |
| Dasabuvir (D) | Yes | OPrD in GT1, OPr in GT4 | OPrD in GT1, OPr in GT4 |
| Elbasvir/grazoprevir (EBR/GZP) | Yes | GT1a, GT1b, GT4 | GT1a, GT1b, GT4 |
| Glecaprevir/pibrentasvir (G/P) | Expected to be approved | Not yet | GT1-6† |
| Sofosbuvir/velpatasvir (SOF/VEL) | No | None | GT1-6† |
| Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) | No | None | GT1-6 with DAA failure†† |
| Peg-interferon with ribavirin (PR) | Yes | GT1-3 | GT2, 3, 5, 6, for whom DAA is not indicated |
| Sof+ribavirin | Yes | GT2, 4 | GT2 |
| Sof+PR | Yes | GT1, GT4 | Not recommended |

KMFD, Korean Ministry of Food and Drug Safety; HIRA, Health Insurance Review and Assessment service.
*Approved state in DEC. 2017, may change during the publication, please refer to website (www.mfds.go.kr) for further information; **Refundable by medical insurance, may change during the publication, please refer to website (www.hira.or.kr) for further information; ***Indicated in 2017 KASL HCV guideline, may differ from medicare covered drug, please refer to website (www.kasl.org) for further information including ribavirin combination and treatment duration; †May differ from each patient with presence or absence of treatment experience, liver cirrhosis or RAS in terms of adding ribavirin, treatment duration; ††Treatment duration may differ from each genotype, presence or absence of treatment experience or cirrhosis, please refer to website (www.kasl.org) for further information include ribavirin combination and treatment duration; †††Treatment indication may differ from each types of DAA failure, please refer to website (www.kasl.org) for further information include ribavirin combination and treatment duration.
had not been previously treated with DAA, were assigned randomly to groups administered SOF/VEL/VOX for 8 wk or SOF/VEL for 12 wk (n=941, LC 18%, IFN-TE patients 23%, except GT3 LC patients) and showed SVR of 95% and 98%, respectively. The SVR of SOF/VEL/VOX treatment for 8 wk compared to SOF/VEL treatment for 12 wk in each GT was as follows: GT1b (97% vs. 97%), GT1a (92% vs. 99%), GT2 (97% vs. 100%), GT3 (99% vs. 97%), GT4 (94% vs. 98%), GT5 (all patients assigned to receive SOF/VEL/VOX, 94%), GT6 (100% vs. 100%).14 In patients without or with LC, the SVR for each treatment group were 96% vs. 98%, and 91% vs. 99%, respectively. The prevalence of baseline NS3 or NS5A RASs was 50% in each group. In patients with baseline RAS, the SVR was 94% and 99% in the SOF/VEL/VOX and SOF/VEL groups, respectively. In a phase 3 study that compared SOF/VEL/VOX therapy for 8 wks with SOF/VEL therapy for 12 wks in GT3 patients with LC (TE 31%), the SVR were 96% and 96%, respectively.14 The results of clinical trials of SOF/VEL/VOX in patients who failed treatment with DAA will be described in each section.

DEFINITION, SPECIAL SITUATION IN KOREA

In Korea, the number of CHC patients who have been treated with first generation DAA, such as boceprevir or telaprevir is very limited. As a result, "treatment experienced (TE)" refers to patients with interferon (or PEG-IFN) with or without ribavirin therapy, unless otherwise mentioned. According to the 2017 KASL guidelines,3 GT1 patients who cannot be sub-typed should be treated as if they were infected with GT1a. Decompensated liver cirrhosis (DC) refers to patients who have Child-Pugh-Turcotte class of more than B or experienced decompensated events. SVR refers to SVR at 12 wk after the end of treatment unless otherwise mentioned.

RAS DETECTION AND INDICATION FOR PRE-TREATMENT ASSESSMENT

Standardized detection of NS5A or drug-specific RAS is not available. However, sequencing of L31 and Y93 mutations in the NS5A region for GT1b patients scheduled for treatment with DCV+ASV was recently approved. For GT1a patients who are scheduled for treatment with EBR/GZR, the RAS test is recommended although it is not approved yet. Patients with "undetermined" RAS test are treated similarly with RASs positive patients. The RAS test for GT3 or GT4 patients is not available in Korea yet.

QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATION IN 2017 KASL GUIDELINE

The quality of evidence was classified according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system.15 The level of evidence was defined as follows; A, the highest level of evidence with the smallest possibility of changes in the conclusion; B, a moderated level of potential changes; and C, the lowest level of evidence with the greatest possibility of changes. The strength of a recommendation was also classified according to the GRADE system. Each study was classified as strong recommendation (1) or weak recommendation (2) based on the quality of evidence, the balance between the desirable and undesirable effect of an intervention, and socioeconomic aspects including cost or availability.

TREATMENT APPROACH TO PATIENTS WITH CHRONIC HEPATITIS C (CHC) AND COMPENSATED LIVER CIRRHOSIS (CC)

The recent updates of the 2017 KASL guidelines regarding treatment for each genotype are summarized in Table 2. The 2017 HCV guidance of AASLD/IDSA are summarized in Table 3. The recommendations of the EASL regarding treatment of hepatitis C 2016 are summarized in Table 4. Different treatment options for the same genotypes from other societies will be discussed.

Treatment of treatment-naïve (TN) and treatment-experienced (TE) GT1b patients with chronic hepatitis C (CHC) and compensated cirrhosis (CC)

The following seven regimens are recommended for the treatment of GT1b patients: LED/SOF regimen for 12 wk (shorter treatment duration to 8 wk may be considered in TN non-cirrhotic patients with HCV RNA less than 6 million IU/mL and without human immunodeficiency virus [HIV]-co-infection) in TN CHC/CC or TE CHC and 12 wk+R or 24 wk for TE patients with CC, EBR/GZR for 12 wk, OPr+D for 12 wk, DCV+SOF for 12 wk for patients without LC and 12 wk+R or 24 wk for patients with LC or DCV+ASV for 24 wk are currently recommended. Although it is not approved in Korea yet, G/P treatment for 8 wk for patients without LC and 12 wk for patients with LC, or SOF/VEL for 12 wk is the one of the other treatment options.

Differently from AASLD and EASL guidelines, DCV+ASV for 24
| GT  | LED/SOF | EBR/GZR | 3D(OPRD), 2D (Opri) | DCV+SOF | DCV+ASV | G/P | SOF/VEL | PR | SOF+R | SOF/VEL/VOX | SOF+EBR/GZR |
|-----|---------|---------|----------------------|---------|---------|-----|---------|----|-------|------------|-------------|
|     | TN      | TE      | TN                  | TE      | TN      | TE  | TN      | TE  | TN    | TE         |              |
| 1b  | CHC     | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 8 wk   | 12 wk      | 12 wk       |
|     | CC      | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 12 wk  | 12 wk      | 12 wk       |
| 1a  | CHC     | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 12 wk  | 12 wk      | 12 wk       |
|     | CC      | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 12 wk  | 12 wk      | 12 wk       |
| 2   | CHC     | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 8 wk   | 12 wk      | 12 wk       |
|     | CC      | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 8 wk   | 12 wk      | 12 wk       |
| 3   | CHC     | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 12 wk  | 12 wk      | 12 wk       |
|     | CC      | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 12 wk  | 12 wk      | 12 wk       |
| 4   | CHC     | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 8 wk   | 12 wk      | 12 wk       |
|     | CC      | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 8 wk   | 12 wk      | 12 wk       |
| 5, 6| CHC     | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 8 wk   | 12 wk      | 12 wk       |
|     | CC      | 12 wk   | 12 wk               | 12 wk   | 12 wk   | 12 wk| 12 wk   | 12 wk| 8 wk   | 12 wk      | 12 wk       |

CHC, chronic hepatitis; CC, compensated liver cirrhosis; TN, treatment-naïve; TE, treatment-experienced; RASs, resistance associated substitutions; wk, weeks; LED/SOF, Ledipasvir/sofosbuvir; EBR/GZR, elbasvir/grazoprevir; 3D(OPRD), ombitasvir/paritaprevir/ritonavir+dasabuvir; 2D(OPi), ombitasvir/paritaprevir/ritonavir; DCV, daclatasvir; SOF, sofosbuvir; VEL, velpatasvir; ASV, asunaprevir; R, ribavirin; G/P, glecaprevir/pibrentasvir; PR, pegylated interferon(PEG-IFN)+ribavirin; VOX, voxilaprevir.

*If Non-LC and HCV RNA <6×10^6 IU/mL and non-HIV infected. **On treatment failure including failure to suppress and breakthrough.
### Table 3. 2017 AASLD/IDSA HCV guidance: treatment of chronic hepatitis C

| GT   | TN | PR fail | Non-NS5A or SOF fail | TN | PR fail | TN | PR fail | TN | PR fail | TN | PR fail | TN | PR fail | TN | PR fail | TN | PR fail | TN | PR fail | TN | PR fail |
|------|----|---------|----------------------|----|---------|----|---------|----|---------|----|---------|----|---------|----|---------|----|---------|----|---------|----|---------|----|---------|
| 1b   | CHC | 12 wk  | 12 wk + R            | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
|      | CC  | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
| 1a   | CHC | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
|      | CC  | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
| 2    | CHC | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
|      | CC  | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
| 3    | CHC | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
|      | CC  | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
| 4    | CHC | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
|      | CC  | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
| 5, 6 | CHC | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |
|      | CC  | 12 wk  |                    | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 12 wk | 12 wk  | 16 w |

CHC, chronic hepatitis; CC, compensated liver cirrhosis; TN, treatment-naive; PI, NS3/4A protease inhibitor; PR fail, PEG-interferon alpha plus ribavirin fail; RASs, resistance associated substitutions; wk, weeks; LED/SOF, Ledipasvir/sofosbuvir; EBR/GZR, elbasvir/grazoprevir; 3D(OPr+D), ombitasvir/paritaprevir/ritonavir+dasabuvir; 2D(OP), ombitasvir/paritaprevir/ritonavir; DCV, daclatasvir; SOF, sofosbuvir; SIM, simeprevir; VEL, velpatasvir; R, ribavirin; G/P, glecaprevir/pibrentasvir; VOX, voxilaprevir.

*If Non-LC and HCV RNA <6×10^6 IU/mL and non-HIV infected; †Not indicated in SIM fail; **On treatment failure including failure to suppress and breakthrough; ***Except NS3/4 protease inhibitor inclusive DAA regimen, NR: not recommended. The shaded part indicated the difference between 2017 KASL and 2017 AASLD/IDSA.
Table 4. 2016 EASL recommendation on treatment of hepatitis C

| GT  | LED/SOF | EBR/GZR | 3D, 2D | DCV+SOF | SOF/VEL | SIM+SOF |
|-----|---------|---------|--------|---------|---------|---------|
|     | TN      | TE      | TN     | TE      | TN      | TE      | TN     | TE      | TN     | TE      |
| 1b  | CHC     | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |
|     | 12 wk   | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |
|     | CC      | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |
| 1a  | CHC     | 12 wk+R/24 wk | 12 wk or 16 wk+R (if HCV RNA>8x10⁵ IU/mL+RAS) | 12 wk or 16 wk+R (if HCV RNA>8x10⁵ IU/mL+RAS) | 3D, 24 wk+R | 12 wk | 12 wk+R/24 wk | 12 wk | 12 wk |
|     | CC      | 12 wk+R/24 wk | 12 wk or 16 wk+R (if HCV RNA>8x10⁵ IU/mL+RAS) | 12 wk or 16 wk+R (if HCV RNA>8x10⁵ IU/mL+RAS) | 3D, 24 wk+R | 12 wk | 12 wk+R/24 wk | 12 wk | 12 wk |
| 2   | CHC     | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |
|     | CC      | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |
| 3   | CHC     | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |
|     | CC      | 12 wk+R/24 wk | 12 wk or 16 wk+R (if HCV RNA>8x10⁵ IU/mL+RAS) | 12 wk or 16 wk+R (if HCV RNA>8x10⁵ IU/mL+RAS) | 3D, 24 wk+R | 12 wk | 12 wk+R/24 wk | 12 wk | 12 wk |
| 4   | CHC     | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |
|     | CC      | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |
| 5,6 | CHC     | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |
|     | CC      | 12 wk   | 12 wk  | 12 wk   | 3D, 12 wk | 12 wk  | 12 wk  | 12 wk  | 12 wk  |

CHC, chronic hepatitis; CC, compensated liver cirrhosis; TN, treatment-naïve; TE, treatment-experienced; RASs, resistance associated substitutions; wk, weeks; LED/SOF, Ledipasvir/sofosbuvir; EBR/GZR, elbasvir/grazoprevir; 3D(OPr), ombitasvir/paritaprevir/ritonavir+dasabuvir; 2D(OPr), ombitasvir/paritaprevir/ritonavir; DCV, daclatasvir; SOF, sofosbuvir; SIM, simeprevir; VEL, velpatasvir; R, ribavirin.

*If TN, Non-LC and HCV RNA<6x10⁵ IU/mL, The shaded part indicated the difference between 2017 KASL and 2016 EASL.
wk is one of treatment options for GT1b patients in Korea (level of evidence and strength of recommendation, A2). A post hoc analysis of a phase 3 clinical study regarding treatment of Asian genotype 1b patients (n=747, including 78 Korean, LC 32%) for 24 wk with ASV plus DCV revealed a SVR of 92%, 79%, 80% in the TN, IFN ineligible, IFN-non-response group, respectively. The presence of baseline NS5A RASs (L31 or Y93) significantly reduced SVR. A pooled data analysis from five clinical studies (n=979, TN 30%, LC 22%) demonstrated a SVR of 39% in patients with NS5A RASs compared to a SVR of 94% in patients without RASs. In this study, the prevalence of NS5A RAS was 13–14%.

Different from the 2015 KASL guidelines, a shorter treatment for 8 wk with LED/SOF can be considered in TN non-cirrhotic GT1b patients with HCV RNA less than 6 million IU/mL and without HIV infection. In a real-life observational cohort study,9 patients who completed 8 wk of LED/SOF treatment had a SVR of 93%, whereas those who completed 12 wk of treatment had a SVR of 97%. In another real-life study, the SVR of TN, GT1b patients without cirrhosis treated for 8 wk with LED/SOF was 99%. In addition, meta-analysis of six real world cohorts comprising of 5,637 patients showed that the relapse rate was comparable between 8- and 12-wk LED/SOF treatments (relative risk, 0.99, 95% CI 0.98–1.00). Based on these data, the 2017 KASL guidelines adopted a shorter LED/SOF treatment for 8 wk in TN non-cirrhotic patients with HCV RNA less than 6 million IU/mL and without HIV infection.

Different from the 2016 EASL guidelines, the treatment duration of the DCV+SOF regimen in LC patients is 12 wk+R or 24 wk. In a cohort study that recruited 768 genotype 1 infected patients (GT1b 46%, LC 73%, TN 16%),20 SVR was assessed according to treatment duration (12 wk vs. 24 wk DCV+SOF with or without ribavirin). In patients with cirrhosis, treated with DCV+SOF for 12 wk, 12 wk+R, 24 wk, or 24 wk+R, SVR were 87% (82/94), 92% (23/25), 94% (323/343), 98% (100/102), respectively (P=0.0152). This study suggested that cirrhosis status and treatment experience influenced SVR. Based on the data, the 2017 KASL guidelines recommended a 12 wk+R or 24 wk DCV+SOF treatment in patients with liver cirrhosis. The 2016 EASL guidelines recommended a 12 wk DCV+SOF treatment in GT1b patients regardless of treatment experience or the presence of cirrhosis.

In AASLD/IDSA HCV guidance, SIM combined with SOF for 12 wk is recommended in GT1b TN or TE CHC.

Treatment of TN and TE GT1a patients with CHC and CC

The following six regimens are recommended with comparable efficacy for the treatment of GT1a patients: LED/SOF treatment for 12 wk (shorter treatment duration to 8 wk may be considered in TN non-cirrhotic patients with HCV RNA less than 6 million IU/mL and non-HIV infected) in TN patients and 12 wk+R or 24 wk for TE patients, EBR/GZR for 12 wk (if RAS+, 16 wk+R), OPr+D+R for 12 wk for patients without cirrhosis and 24 wk for patients with cirrhosis, DCV+SOF for 12 wk for patients without cirrhosis and 24 wk or 12 wk+R for patients with cirrhosis. Although it is not approved in Korea yet, G/P treatment for 8 wk for patients without cirrhosis and 12 wk for patients with cirrhosis, or SOF/VEL for 12 wk is the one of the other treatment options.

Different from the AASLD guidelines, LED/SOF 12 wk+R or 24 wk is recommended for TE GT1a chronic hepatitis patients without cirrhosis in 2017 KASL guidelines. A previous study21 regarding TE patients (n=440, GT1a 79%, LC 20%), under LED/SOF treatment for 12 wk, 12 wk+R, 24 wk, or 24 wk+R showed no major differences in SVR; 94% (102/109), 96% (107/111), 99% (108/109), 99% (110/111) in each group, respectively. In patients with cirrhosis, SVR was 86% (19/22), 82% (18/22), 100% (22/22), 100% (22/22) respectively. Accordingly, AASLD recommended LED/SOF treatment for 12 wk without ribavirin for chronic hepatitis and 12 wk with ribavirin for LC patients. In GT1a patients, the presence of baseline NS5A or LED specific RASs significantly reduced SVR. In GT1a patients, SVR of LED/SOF was 76% (22/29) in patients with LED-specific RAS, which is lower than the 97% (409/420) observed in patients without LED-specific RAS.22 In LC patients, SVR was 77% (10/13) and 96% (216/224) in patients with or without LED-specific RAS, respectively. Even in patients without cirrhosis, SVR was 75% (12/16) and 98% (193/196) in patients with or without LED-specific RAS. The prevalence of LED-specific RAS and NS5A RAS was reported up to 8.3% and 13.0%, respectively.23 In addition, the RAS test for GT1a is not available in Korea. Accordingly, the 2017 KASL guidelines suggested the addition of ribavirin to 12 wk LED/SOF therapy or the extension of LED/SOF therapy to 24 wk in TE GT1a patients with or without cirrhosis.

As described previously, the 2017 KASL guidelines recommend a 12 wk+R or 24 wk DCV+SOF treatment in GT1a patients with liver cirrhosis. The 2016 EASL guidelines recommended a 12 wk treatment with DCV+SOF in TN GT1a patients with cirrhosis and a 12 wk +R/24 wk in TE patients without cirrhosis. SIM combined with SOF for 12 wk is recommended in TN and TE GT1a non-cirrhotic patients in AASLD/IDSA HCV guidance.

Treatment of TN and TE GT2 patients with CHC and CC

The following five regimens are available for GT2 patients: SOF+R
12 wk for TN & TE patients with CHC, 16wk for TN LC patients and 16–24 wk for TE LC patients or DCV+SOF 12 wk. G/P treatment for 8 wk for patients with CHC and 12 wk for patients with CC or SOF/VEL for 12 wk is one of the other treatment options although they are not approved in Korea yet. PR 24 wk for TN patients may be considered if there is no available DAA treatment option (e.g. chronic kidney disease, CKD).

Different from the treatment guidelines from other continents, SOF+R is the only regimen covered for payment under the medical care benefits for GT2 patients in Korea. Previous studies from western countries have shown that the SVR of SOF+R treatment for 12 wk in TN GT2 patients with CHC was 96–98%. In patients with cirrhosis, studies for the optimal duration of SOF+R are very limited. SVR of 12 wk, 16 wk or 20 wk treatment with SOF+R in LC were 72–100%, 95–100% and 91% although that was not a direct comparison. In a real-life study in Europe (TE 30.5%, LC 26.8%, DC 11%), the overall SVR of 12 wk/16 wk SOF+R treatment was 88.2%. In non-cirrhotic patient, SVR of 12 wk or 16wk treatment is 91% and 92.9%. In patients with LC treated of 12 or 16wk, SVR was 79.0% and 83%. In another real-life study (TE 43%, LC 58%), 12 wk treatment with SOF+R in patients with advanced fibrosis (n=123) or 16 wk/20 wk treatment in patients with LC (n=168) showed SVR of 95%. In patients with LC treated for 16 wk or 20 wk, SVR was 95% (86/91) and 91% (75/82).

In Korea, the SVR of 12-wk SOF+R treatment was 98% (177/181) in TN and 97% (32/33) in TE patients without liver cirrhosis. In patients with CC, the SVR of 16-week SOF+R treatment was 96% (50/52), although it is not possible to distinguish between TN and TE patients.

Regarding DCV+SOF, the 2017 KASL guidelines recommended a 12 wk treatment for both TN and TE, non-LC and LC patients which is different from the AASLD guidelines, which recommended a 12 wk therapy for non-LC and 16–24 wk therapy for LC patients. There are only a few studies regarding DCV and SOF therapies in patients with GT2. In phase 2 studies of 24 wk DCV+SOF treatment, the SVR was 92% (24/26) in TN patients. Based on sub-group analysis of genotype 2 patients in a real-life study (GT1-4, n=2,612, TE 53%), DCV+SOF therapy for 12 wk showed a SVR of 95% (18/19) in non-LC patients, DCV+SOF+R for 12 wk showed a SVR of 92% (121/131) in patients with liver cirrhosis although it is not possible to distinguish between the TN and TE patients. In a real life study regarding DCV+SOF therapy for 12 or 24 wk (TE 47%, DC 20%, ribavirin combination 86% and 78%) in patients with LC, the SVR was 92% (34/37) and 95% (89/94), respectively. The overall SVR in TN and TE patients was 93% and 94%, respectively. In Korea, the RAS test for GT3 patients is not available. Based on these results and the challenges to treat GT3 LC patients, the 2017 KASL guidelines recommended a 12 wk DCV+SOF therapy for TN CHC patients, a 12wk+R therapy for TE CHC patients and a 24 wk+R therapy for TN- and TE-LC patients.

In a phase 3 study comparing SOF/VEL treatment for 12 wk and SOF+R for 12wk, SVR were as follows: TN CHC (98% vs. 90%), TN LC (93% vs. 73%), TE CHC (91% vs. 71%) and TE LC (89% vs. 58%). Of the 274 SOF/VEL treated patients, the prevalence of NS5A RAS was 16%. In patients with or without RAS, SVR was 88% (38/43) and 97% (225/231), respectively. Moreover, the SVR in patients with Y93H was 84% (21/25). In Korea, the RAS test for GT3 patients is not available. Combination of ribavirin with SOF/VEL is recommended for TE CHC and TN- and TE-LC patients.

In a phase 2 study examining G/P treatment for 12 or 16 wk in TE patients without liver cirrhosis and for 16 wk in TE patients with liver cirrhosis (54% PR, 46% SOF+R with or without peg-IFN), SVR were 91% (20/22), 96% (21/22) and 96% (45/47), respectively.
Different from the 2017 KASL guidelines, the AASLD guidelines recommend SOF/VEL/VOX 12 wk for Y93-positive TN LC patients and Y93-positive TE CHC- or LC-patients. In a phase 3 study comparing SOF/VEL/VOX treatment for 8 wk with SOF/VEL for 12 wk in GT 1–6 patients (for GT3, 77% of the patients were TN with no liver cirrhosis), the SVR of GT3 patients was 99% (91/92) and 97% (86/89), respectively. In a phase 3 study comparing SOF/VEL/VOX treatment for 8 wk and SOF/VEL for 12 wk in genotype 3 patients with liver cirrhosis (IFN experienced 31%), the SVR was 96% (106/110) and 96% (105/109), respectively.

**Treatment of TN and TE GT4 patients with CHC and CC**

The following six regimens are recommended for GT4 patients. LED+SOF treatment for 12 wk for TN patients and 12 wk+R or 24 wk for TE patients, EBR/GZP for 12 wk for TN patients and for those with previous IFN-based treatment relaper and 16wk+R for patients with previous on-treatment failure (including failure to suppress and breakthrough), OP/r+R for 12 wk, DCV+SOF for 12 wk for patients without cirrhosis and 24 wk or 12 wk+R for patients with cirrhosis. G/P treatment for 8 wk for patients without cirrhosis and for 12 wk for patients with cirrhosis or SOF/VEL for 12 wk is one of the other treatment options although they are not approved in Korea yet.

Different from the AASLD/IDSA guidelines, the KASL guidelines recommend LED+SOF treatment for 12 wk+R or 24 wk in TE CHC and LC patients. One phase 2 clinical trial using LED+SOF for 12 wk in 21 CHC patients (7 LC, 8 TE) showed a SVR of 95%. Another phase 2 trial with the same treatment in 44 CHC patients (10 LC, 22 TE) showed a SVR of 93%. Although the evidence is not robust yet, addition of ribavirin to 12 wk LED+SOF treatment or extension of treatment duration to 24 wk is recommended in these patients to improve SVR.

Different from the AASLD/IDSA guidelines, DCV+SOF treatment is one of the options for GT4 patients according to the KASL guidelines. In a retrospective study on 47 genotype 4 CHC patients, DCV+SOF treatment for 12 wk showed a SVR of 100% (32/32). In another retrospective study including 176 GT4 CHC patients (TE 82%, LC 76%), DCV+SOF with or without ribavirin for 12 or 24 wk showed 90% of SVR in total. In patients with cirrhosis, the SVR of DCV+SOF therapy with or without ribavirin was 97%, 88% respectively.

Currently released HCV guidance in USA recommended LED/SOF treatment 12 wk for TN-CHC & -LC, TE CHC patient and 12 wk+R in TE LC patients. DCV+SOF is not recommended in GT4 patients. According to EASL 2016 guidelines, SIM+SOF are recommended in GT4 patients.

There are five available regimens for the treatment of GT5 and GT6 patients. LED+SOF treatment for 12 wk in TN and for 12 wk+R or 24 wk in TE patients, or DCV+SOF for 12 wk in TN and 12 wk+R or 24 wk in TE patients. G/P treatment for 8 wk in patients without cirrhosis and 12 wk for patients with cirrhosis or SOF/VEL for 12 wk is one of the other treatment options although they are not approved in Korea yet. PR for 24 wk may be considered if there is no available DAA treatment option for TN patients (i.e. CKD).

Different from the AASLD guidelines, LED+SOF treatment for 12 wk+R or 24 wk is recommended for TE-GT5 and -GT6 patients in KASL guidelines. A phase 2 clinical trial using LED/SOF for 12 wk in 41 GT5 patients (9 LC, 20 TE) showed a SVR of 95% (39/41) and another study with the same regimen in 25 GT6 patients (2 LC, 2 TE) showed a SVR of 96% (24/25). Different from the AASLD guidelines, DCV+SOF is one of the treatment option for GT5 and GT6 patients in KASL guidelines. In a retrospective study, DCV+SOF treatment for 12 or 24 wk showed a SVR of 100% for both GT5 (25/25) and GT6 (5/5) patients.

According to the AASLD/IDSA HCV guidance, LED/SOF treatment for 12 wk is recommended for TN and TE patients, whereas DCV+SOF is not recommended for GT5 and GT6 patients.

**TREATMENT APPROACH TO PATIENTS WITH DECOMPENSATED LIVER CIRRHOSIS (DC)**

The following three regimens are recommended for the treatment of GT1, GT4, GT5 and GT6 decompensated LC patients: LED+SOF for 12 wk+R (starting from 600 mg) or 24 wk, DCV+SOF for 12 wk+R (starting from 600 mg) or 24 wk, VEL/SOF for 12 wk+R (weight based ribavirin) or 24 wk is one of the other option although it is not approved in Korea yet.

There are two available regimens for the treatment of GT2 and GT3 DC patients: DCV+SOF for 12 wk+R (starting from 600 mg) or 24 wk and VEL/SOF for 12 wk+R (weight based ribavirin) or 24 wk although they are not approved in Korea yet.

In a multicenter randomized controlled trial of 108 patients with HCV genotypes 1 and 4 with DC (CTP class B or C, CTP scores ≤ 12), patients were randomly assigned to receive a daily fixed-dose combination of LED/SOF with ribavirin (initial dose of 600 mg, increased as tolerated) for 12 or 24 wk. SVR of 12 wk or 24 wk in patients with CTP class B was 87% and 89%. In CTP class C patients, SVR of 12
wk or 24 wk was 86% and 87%. \(^{38}\)

In a phase 3 trial, DCV+SOF+R treatment (initial low dose of 600 mg) for 12 wk to sixty decompensated LC patients (HCV GT 1 : 3 : 2/4/6=45:6:9), resulted in an overall SVR of 83%. SVR were 76% and 100% among patients with HCV GT1a and 1b, respectively. In patients with HCV GT1, SVR were 92% and 50% for patients with CTP class B and C, respectively. Among subjects with HCV GT3 and GT2/4/6, SVR12 rates were 83% and 89%, respectively. \(^{39}\)

In a multicenter, open-label trial that included 267 previously treated and untreated patients with CTP class B (GT1a/1b/GT2/3/GT4/GT6, 159/48/12/39/8/1), participants were randomly assigned to receive SOF/VEL treatment for 12 wk, 12 wk+R, or 24 wk. SVR was 88%, 94% and 93% in patients with GT1a, and 89%, 100% and 88% in patients with GT1b, respectively. For patients with GT2, the corresponding SVR were 100%, 100% and 75%, while for patients with GT3, SVR were 50%, 85%, 50%, respectively. Among patients with HCV GT4, all (100%) achieved SVR to SOF/VEL-based regimens. \(^{40}\)

In AASLD/IDSA guidance, DCV+SOF is only recommended for GT1 or GT4 patients.

**TREATMENT APPROACH FOR PATIENTS WITH LIVER TRANSPLANTATION (LT) OR OTHER EXTRA-HEPATIC ORGAN TRANSPLANTATION**

The following four regimens are recommended for the treatment of GT1 post LT patients: LED+SOF for 12 wk+R or 24 wk, DCV+SOF for 12 wk+R (starting from 600 mg) or 24 wk, G/P for 12 wk (if compensated) and OPrD for 24 wk+R (if F0-F2). The following three regimens are recommended for the treatment of GT2 post LT patients: DCV+SOF for 12 wk+R (starting from 600 mg) or 24 wk, G/P for 12 wk (if compensated) and SOF+R for 24 wk. The following two regimens are recommended for the treatment of GT3 post LT patients: DCV+SOF for 12 wk+R (starting from 600 mg) or 24 wk and G/P for 12 wk (if compensated). The following three regimens are recommended for the treatment of GT4, GT5 and GT6 post LT patients: LED+SOF for 12 wk+R or 24 wk, DCV+SOF for 12 wk+R (starting from 600 mg) or 24 wk and G/P for 12 wk (if compensated).

In a multicenter, randomized controlled trial, patients treated with LED/SOF+R for either 12 or 24 wk, including GT1 or GT4 LT recipients (n=229), SVR in stages F0 to F3 were 96% and 98% in the 12- and 24-wk arms, respectively. Patients with compensated cirrhosis showed a SVR of 96% in both the 12- and 24-wk arms. SVR was lower in patients with CTP class B LC (SVR 85% vs. 88% in the 12- and 24-wk arms) or CTP class C cirrhosis (60% vs. 75% in the 12- and 24-wk arms). \(^{38}\) In the open-label DCV+SOF+R (initial dose, 600 mg) for 12 wk in patients with recurrent HCV infection post-transplantation (n=53, HCV GT 1:3:6=41:11:1), the overall SVR was 94%. In GT1, GT3, and GT6, SVR were 95% (39/41), 91% (10/11), and 100% (1/1) respectively. \(^{40}\)

The safety and efficacy of the 12 wk G/P treatment was investigated in 100 patients (GT 1/2/3/4=6, 57%/13%/24%/6%) who developed recurrent HCV infection (F0-1 80%, F2 6%, and F3 14%) after LT (n=80) and renal transplantation (n=20). The overall SVR was 98% after 12wk of G/P therapy. \(^{41}\)

A study, involving 34 LT recipients (29 GT1a) with no fibrosis or with mild fibrosis (Metavir fibrosis stage F0-F2) of GT1 patients, examined the use of fixed-dose combination OPr plus twice-daily dose of dasabuvir and weight-based ribavirin for 24 wk and reported a SVR of 97% (33/34). \(^{42}\)

In a pooled analysis of 10 studies with 333 patients with renal transplantation (GT1 88%, TN 63%, LC 25%) receiving 12–24 wk of DAA therapy, SOF-based regimens were the most frequently used DAAs for recurrent hepatitis C after renal transplantation. The overall SVR in post-renal transplant patients treated with DAA was 94.2%. SVR was 67% (10/15) in combination with SOF+R, 75% (3/4) in combination with DCV+SOF, and 98% (158/161) in combination with LED/SOF with or without ribavirin. \(^{43}\)

According to the AASLD treatment guidelines, for the treatment of GT1, GT4, GT5 and GT6 patients, LED+SOF+R treatment for 12 wk or G/P for 12 wk for non-LC patients, LED+SOF+R for 12 wk for CC patients can be considered. Alternatively, DCV+SOF+R (initial dose, 600 mg) for 12 wk, or SIM+SOF±R for 12 wk (for GT1, 4 only) or G/P for 12 wk in patient without LC or with CC can be considered. For DC with GT1, 4, 5, 6, LED/SOF+R (initial dose, 600 mg) for 12 wk can be considered. For non-cirrhotic GT2 and GT3 patients, G/P for 12 wk, or DCV+SOF+R (initial dose, 600 mg) for 12 wk can be considered; For GT2 or GT3 patients with compensated cirrhosis, DCV+SOF+R (initial dose, 600 mg) for 12 wk or alternatively G/P for 12 wk, or SOF/VEL+R for 12 wk can be considered. In decompensated cirrhosis GT2 or GT3 patients, DCV+SOF+R (initial dose, 600 mg) for 12 wk or SOF/VEL+R for 12 wk can be considered.

**TREATMENT APPROACH TO PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD)**

The following three regimens are recommended for GT1 patients with estimated GFR (eGFR) less than 30 mL/min: EBR/GZR, OPrD (if
GT1a, add ribavirin 200 mg/d and G/P. In GT1b patients, DCV+ASP for 24 wk may be considered. For GT2, GT3, GT4, GT5, GT6 patients with eGFR less than 30 mL/min, G/P can be recommended. For GT4 patients with eGFR less than 30 mL/min, EBR/GZR or OPrD+ ribavirin 200 mg/d can be considered. For GT2, GT3, GT5, GT6 patients with eGFR less than 30 mL/min with no indication for DAA, PR at reduced dose may be considered. In patients undergoing dialysis, PEG-IFN without ribavirin may be considered.

In genotype 1 HCV-infected patients with eGFR less than 30 mL/min (n=20, 1a 65%) regardless of dialysis, OPr+D with ribavirin (200 mg/day, GT1a) or without ribavirin (GT1b) for 12 wk resulted in SVR of 90% (18/20) without dose modification. In GT1 HCV-infected patients with eGFR less than 30 mL/min (n=235, 1b 48%, TN 80%, LC 6%) regardless of dialysis, EBR/GZR for 12 wk resulted in SVR of 99% without dose modification. In patients with GT1-6 HCV infection and renal impairment of variable degree, G/P for 8–12 wk without dose modification resulted in SVR rates of 98%.

In a retrospective Japanese study, DCV+ASV for 24 wk in dialysis-treated GT1b patients resulted in SVR of 100% without dose modification, and there was no significant adverse event. The dose for ASV should be reduced and prescribed at 100 mg daily in non-dialysis patients with eGFR less than 30 mL/min. Dose adjustment of PEG-IFN-α and ribavirin is required depending on the severity of kidney disease, because clearance is reduced according to the degree of impaired kidney function. The recommended treatment for patients with severe renal impairment (eGFR of 15–59 mL/min) is 135 μg of PEG-IFN-α-2a or 1 μg/kg of PEG-IFN-α-2b together with 200–800 mg/day of ribavirin twice per day with a gradual increase in dose. Patients on dialysis may be treated with either interferon alpha or PEG-IFN-α; however, combination with ribavirin is not recommended.

According to AASLD/IDSA, EBR/GZR treatment for 12 wk is recommended for GT1 and GT4 patients. G/P treatment for 8–16 wk is recommended for GT1, GT2, GT3, GT4, GT5 and GT6 patients with severe (eGFR less than 30 mL/min) or end stage CKD without dose adjustment.

### TREATMENT APPROACH FOR PATIENTS WHO FAILED PREVIOUS DAA TREATMENT

For patients who failed previous DAA treatment, recommended regimens depends on previous treatment experience. SOF/VEL/VOX and G/P are currently unavailable in Korea although some drugs may be prescribable in the future.

For patients who failed previous NSSA containing DAA, following 4 options are recommended: SOF/VEL/VOX 12 wk for GT1-6, G/P 16 wk for GT1 (G/P is recommended in patients who have been treated with regimens containing NSSA or NS3/4A PI, but not both), alternatively SOF+EBR/GZR 12 wk+R for GT1 or SOF+OPrD for GT1 (GT1a, 12 wk+R for CH, 24 wk+R for LC; GT1b, 12 wk).

For patients who failed previous non-NSSA containing DAA, following 3 options are recommended: SOF/VEL/VOX 12 wk for GT1-4, G/P 12 wk for GT1 (G/P is recommended in patients who have been treated with regimens containing NSSA or NS3/4A PI, but not both). In GT1b or GT2, SOF/VEL treatment for 12 wk is an alternative treatment option.

For patients who failed previous SOF-containing DAA, following 5 options are recommended: SOF/VEL/VOX 12 wk for GT1-4, G/P 12 wk for GT1, 2, 4, 5, 6 and 16 wk for GT3. For GT1 patients, LED/ SOF (12 wk+R for CH and 24 wk+R for LC) can be considered. DCV+SOF 24 wk+R for GT2 and GT3 patients, SOF+EBR/GZR 12 wk for GT3 is one of the alternative options although the evidence is not strong.

The SVR was 70% after 12 wk re-treatment with LED/SOF in 54 patients with genotype 1b CHC who did not respond to DCV+ASP treatment for 24 wk. Twenty-five genotype 1 HCV infected patients (22 GT1a, 3 GT1b, and 5 with cirrhosis) who failed the short-term combination therapy with SOF+EBR/GZR for 4, 6 or 8 wk were retreated with SOF+EBR/GZR and ribavirin for 12 wk. The overall SVR rate was 100% (25/25) and all patients with baseline NS3 RAS (17 patients) and NSSA RAS (14 patients) achieved SVR. Twenty-two GT1 infected HCV patients (20 GT 1a, 2 GT1b, 6 LC) who failed the previous DAA treatment (14 OPrD, 2 OPr) were treated with SOF+OPrD with or without ribavirin. The overall SVR was 95% (21/22). In GT1a patients, SVR of SOF+OPrD+R treatment for 12 wk in non-LC patients and for 24 wk in LC patients was 92% (13/14) and 100% (7/7), respectively. In GT1b patients, SVR of SOF+OPrD treatment for 12 wks was 100% (2/2). All 18 patients with baseline RAS achieved SVR.

A total of 263 patients with HCV infection (101 GT1a, 45 GT 1b, 4 other GT1, 5 GT 2, 78 GT3, 22 GT4, 1 GT5, 6 GT6, 1 unknown, 121 with LC) who failed in previous DAA treatments including the NSSA inhibitor (161 NSSA and NS5B inhibitor, 83 NSSA and NS3 inhibitor, 18 NSSA inhibitor) were treated with SOF/VEL/VOX for 12 wk. The overall SVR was 96% (253/263). SVR of genotype 1a and 1b were 96% (97/101) and 100% (45/45), respectively. The SVR of genotype 2, 3, 4, 5, and 6 was 100% (5/5), 96% (74/78), 91% (20/22), 100% (1/1), and 100% (6/6), respectively. The SVR of patients without baseline RAS was 98% (42/43), and the SVR of pa-
tients with RAS was 97% (199/205). The SVR of 121 patients with cirrhosis was 93% (113/121).51

In a total, 333 patients with HCV infection (98 GT1a, 46 GT1b, 64 GT2, 106 GT3, 19 GT4, 153 with LC) who failed in previous non-NSSA DAA treatments (243 NSSB inhibitors, 84 NSSB+NS3 inhibitors, 5 NS3 inhibitors) were treated with either SOF/VEL/VOX or SOF/VEL for 12 wk.51 The overall SVR was 98% (178/182) and 90% (136/151) respectively. The SVR for each genotype for SOF/VEL/VOX or SOF/VEL treatment were as follows; GT1a (98% vs. 89%), GT1b (96% vs. 95%), GT2 (100% vs. 97%) and GT3 (96% vs. 85%). All 19 patients with genotype 4 who were treated with SOF/VEL/VOX for 12 wk achieved SVR (100%). All 83 patients with baseline NS3 or NS5A RAS who were treated with SOF/VEL/VOX achieved SVR. The SVR of patients treated with SOF/VEL without or with baseline RAS was 89% (67/75), 90% (63/70), respectively.51

A total of 50 GT1 HCV infected patients without cirrhosis (42 GT1a, 8 GT1b) who failed previous DAA treatments (25 NS3 inhibitors, 8 NSSA inhibitors, 17 NS3 inhibitors and NSSA inhibitors), were treated with G/P with or without ribavirin for 12 wk. The overall SVR was 92% (46/50).52 Ninety-one patients with CHC (67 GT1a, 18 GT1b, 2 other GT4, 27 LC) who had failed previous DAA treatments (34 NSSA inhibitors, 27 NS3 inhibitors, 30 NS3 and NS5A inhibitors), were treated with G/P for 12 or 16 wk. Overall, the SVR was 89% (39/44) and 91% (43/47), respectively.53 In patients who failed previous NS3 inhibitor treatment, SVR for 12 or 16 wk of treatment were 100% (14/14) and 100% (13/13). In patients who failed previous NSSA inhibitor treatment, SVR of each treatment duration was 88% (14/16) and 94% (17/18). In patients who failed previous NS3 and NS5A inhibitor treatment, SVR of 12- or 16-wk G/P treatment is 79% (11/14) and 81% (13/16). In patients without baseline RAS, SVR of 12 and 16 wk of G/P was 100% (13/13) and 100% (13/13), respectively. In patients with NS3 RAS, SVR was 100% (2/2) and 100% (4/4). In patients with NSSA RAS, SVR was 83% (20/24) and 96% (22/23). In patients who both have of NS3 and NSSA RAS, SVR was 80% (4/5) and 25% (1/4), respectively.53 Therefore, based on the clinical results so far, G/P seems to have a limited efficacy in patients who have both of NS3 RAS and NSSA RAS.

The SVR of 12 wk of treatment with LED/SOF 24 wk was 100% in 14 patients with GT1 CHC (8 GT1a, 6 GT1b) who failed the SOF+R treatment for 24 wk.54 Fifty-one patients (30 GT1a, 20 GT1b, 1 GT3a, 14 with LC) who failed previous HCV therapy (25 SOF+PR, 20 SOF+R, 6 PR) were treated with LED/SOF+R for 12 wk. The SVR was 98% (50/51).55 A total of 52 patients with CHC (44 GT1, 2 GT2, 4 GT3, 3 GT4) who had previous treatment experience were treated with DCV+SOF for 12 wk. The SVR was 98% (51/52), however the number of patients with GT2 and GT3 was very limited.56 In a study of genotype 3 patients treated with DCV+SOF for 12 wk, patients with prior treatment experience with SOF and ribavirin combination or SOF+PR did not show satisfactory SVR (71%, 5/7).57 Based on these limited SVR of 12 wk combination, DCV+SOF+R for 24 wk may be an alternative option.

In a genotype 3 CHC patient with cirrhosis, 53 patients who failed previous treatment (including 2 SOF+R therapy) were treated with EBR/GZR and SOF for 12 wk, or with EBR/GZR+SOF with ribavirin for 12 wk, or with EBR/GZR+SOF with ribavirin for 16 wk. The SVR were 100% (17/17), 94% (17/18) and 94% (17/18), respectively.57

In GT 1, 2, 4, 5, and 6 CHC patients without cirrhosis, patients were treated with G/P for 8 or 12 wk.58,59 The SVR was 97–99% and 99–100% for 8 and 12 wk of treatment, respectively. A total of 146 patients with genotype 1, 2, 4, 5, and 6 CHC patients with cirrhosis (including 36 TE patients and 11 patients who had SOF-based treatment) were treated with G/P for 12 wk and the SVR was 99%.60 A total of 131 patients with genotype 3 CHC were treated with G/P for 12 or 16 wk. Among them, 91 TE patients (including 42 patients with SOF-based treatment) were included. SVRs of 12 wk treatment in patients without cirrhosis, 16 wk treatment in patients without cirrhosis, and 16 wk treatment in patients with cirrhosis were 91% (20/22), 96% (21/22) and 96% (45/47), respectively.61

According to the currently released AASLD/IDSA HCV guidance, treatment recommendations are follows as; for non-LC or LC GT1 patients who failed NSSA-containing regimen, SOF/VEL/VOX 12 wk or G/P 16wk (except for the PI-containing DAA regimen). For non-LC GT1 patients who failed non-NSSA or SOF-containing regimen, SOF/VEL/VOX 12 wk or G/P 12 wk for GT1a patients and G/P 12 wk or SOF/VEL 12 wk for GT1b patients, or LED/SOF+R 12 wk can be considered. For LC GT1 patients who failed non-NSSA or SOF-containing regimen, SOF/VEL/VOX 12 wk or G/P 12 wk for GT1a patients and G/P 12 wk or SOF/VEL 12 wk for GT1b patients, or LED/SOF+R 12 wk can be considered. For GT2 with SOF experienced patients, SOF/VEL 12 wk or G/P 12 wk is recommended. For GT3 DAA experienced patients, SOF/VEL/VOX treatment 12 wk and 12 wk+R for LC with NSSA failure is recommended. For GT4, 5, 6 who failed previous DAA treatment, SOF/VEL/VOX 12 wk is recommended.

Conflicts of Interest

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