



Editorial

Does the old-fashioned sofosbuvir plus ribavirin treatment in genotype 2 chronic hepatitis C patients still works for Koreans?

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According to the 2017 Korean Association for the Study of the Liver (KASL) treatment guidelines of chronic hepatitis C,¹ treatment options for genotype 2 patients are sofosbuvir plus ribavirin (SOF+R), SOF plus daclatasvir, glecaprevir plus pibrentasvir, SOF plus velpatasvir and pegylated interferon alpha plus ribavirin (PEG-IFN+R). Except in cases where only patients who cannot use the direct acting antivirals (DAAs), PEG-IFN+R is replaced by DAAs.

In reality, there are two possible DAA treatment options, SOF+R (daily 400 mg of SOF+1,000 or 1,200 mg/d of ribavirin if body weight less or over than 75 kg) which can get insurance benefits and glecaprevir plus pibrentasvir which could not be used at the start of the study, those are currently available or are likely to be available for genotype 2 in Korea.

But in other continents, SOF+R treatment is no longer recommended because of frequent side effects of ribavirin and somewhat lower sustained virologic response (SVR) rate than other DAA combinations.^{2,3}

Regarding SVR rate of SOF+R treatment, previous studies conducted in Western countries have shown that SVR rates in the order of 80-95%.⁴⁻⁷ In a trial for the treatment-naïve genotype 2 patients comparing 12 weeks of SOF+R with 24 weeks of PEG-IFN+R,⁴ SVR rate was 97% and 78% in each treatment group. In patient with and without liver cirrhosis, SVR rates were 91% and 98%, respectively. For patients ineligible or intolerant to PEG-IFN+R, SOF+R treatment achieved 93% of SVR.⁶ In IFN non-responders, 12- or 16-weeks of SOF+R treatment leads to 86% and 94% of SVR, respectively. In that study, SVR rates were 60% and 78% in patients with cirrhosis treated for 12- and 16-weeks of SOF+R treatment, respectively. In another study including genotype 2 treated with 12 weeks of SOF+R,⁵ SVR rates were 97%, 100%, 94%, and 78% in treatment-naïve non-cirrhotics, treatment-naïve cirrhotics, treatment-experienced non-cirrhotics, and treatment-experienced cirrhotics, respectively.

These results suggested that treatment-experienced patients with cirrhosis may benefit from more than 12 weeks of therapy.

A real-world study showed that SVR rates of 12 or 16-week of SOF+R for treatment-naïve genotype 2 cirrhotics were 72% and 100%, respectively.⁸ In treatment-experienced cirrhotic patients,

Abbreviations:

DAAs, direct acting antivirals; KASL, Korean Association for the Study of the Liver; PEG-IFN, pegylated interferon alpha; R, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response

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SVR rates were 87% and 77% in 12- or 16-weeks treated group, respectively. In another real-world experience including 16- or 20-weeks of SOF+R for cirrhotics (including 51% of treatment experience), SVR rates were 95% and 91%, respectively.⁹ An open-label phase 3 study including treatment-experienced genotype 2 cirrhotic patients has shown that SVR rates were 87% and 100% for those receiving 16- and 24-weeks of SOF+R, respectively.¹⁰

Unlike the findings in the Western countries, studies conducted in Asia have shown that 12-week SOF+R leads to SVR rates of 96-100%, regardless of treatment experience or presence of cirrhosis.¹¹⁻¹³

In a phase 3b study conducted in Korea (treatment-experienced patients 18%, liver cirrhosis 10%),¹¹ the overall SVR rate following 12 weeks of SOF+R was 97%, and all of treatment-experienced patients including cirrhotics achieved SVR of 100%. In another Korean real-life study,¹⁴ the SVR rates following 12 weeks of sofosbuvir and ribavirin were 98% (177/181) in treatment-naïve patients without liver cirrhosis and 97% (32/33) among treatment-experienced patients without liver cirrhosis. The SVR rate after 16 weeks of sofosbuvir and ribavirin therapy was 96% (50/52) in patients with liver cirrhosis, although it was not possible to distinguish between treatment-naïve and treatment-experienced patients in that analysis.

In a phase 3 study conducted in Taiwan (treatment-experienced patients 50%, liver cirrhosis 15%),¹² the SVR rate following 12 weeks of SOF+R was 100%, regardless of treatment experience or presence of cirrhosis. In a Japanese study,¹³ the SVR rate following 12 weeks of SOF+R was 97%. The SVR rates of treatment-naïve and treatment-experienced patients were 98% and 95%, respectively. Among them, all of eight treatment-naïve patients and 8 of 9 treatment-experienced cirrhotics achieved SVR. Overall, 16 of 17 patients (94%) with cirrhosis achieved SVR.

Regarding SOF+R drug safety, the combination of SOF and ribavirin exhibited acceptable safety profiles. The rate of premature discontinuation because of adverse events was 1-2%, that was not different from the placebo group. Adverse events associated with ribavirin including fatigue, insomnia, pruritus, and anemia were more frequent. The rate of moderate to severe adverse events (Grade 3 or 4) was 1-6%.⁴⁻⁶

In this issue of *Clinical and Molecular Hepatology*, the retrospective study by Kim et al. including 163 genotype 2 patients (liver cirrhosis 30%, treatment-experienced patients 12%) treated with SOF+R for 12- or 16- weeks adjusted for presence of cirrhosis showed high SVR rate of 98.8% (161/163).¹⁵ Among 49 liver cirrhotic patients, 18 patients were treated for 12 weeks and all of

them achieved SVR. Except one patient who stopped the treatment after 2 weeks of treatment because of severe anemia, only one treatment-naïve, non-cirrhotic patient showed relapse. Adverse events during the treatment were reported in 16% of patients. Eleven percent of patients needed to reduce ribavirin dosage because of anemia. Although this retrospective multicenter study has limitations, the authors concluded that 12- or 16 weeks of SOF+R was effective and well tolerated in both of treatment-naïve and treatment-experienced Korean genotype 2 patients with or without cirrhosis.

As aforementioned, the studies conducted in Western countries have shown that overall SVR rate approximated 80-95% in Europe and North America. In contrast, SVR rates in Asia were closer to 100%. It is unclear why the Westerns and Asians show different treatment response, but it can be explained as follows: When the baseline characteristics between studies from Western and Asian countries were compared, the average age and the rate of baseline high viral load were similar. The average body mass index (BMI) was 26-29 in the pivotal trials⁴⁻⁶ and 24 in Korea.¹¹ In VALENCE study including SOF plus ribavirin for genotype 2,⁵ patients with baseline BMI less or more than 30 had 97% and 75% of SVR, respectively. In that study, patients with- or without ribavirin dose reduction/interruption had SVR rates of 100% and 93%, respectively. On the contrary, FISSION study⁴ including SOF plus ribavirin for genotype 2 had shown that ribavirin exposure was a significant factor for SVR (odds ratio 1.258). Kim et al.'s study did not include data of baseline BMI and prior ribavirin-exposure in their study populations.¹⁵ Men comprised 55-71% of the total patients included in the pivotal trials and 35-41% in Korean study.

Also, another even more remarkable difference was that the IFNL4 gene (previous mistakenly refer to IL28B, rs12979860) C/C constituted the 33-47% of total study population in the pivotal study patients.^{4,5} It is a strong predictor of response to PEG-IFN-based therapy.¹⁶ Individuals with the favorable C/C allele have about a 2-fold higher likelihood of achieving SVR compared to individuals with C/T or T/T genotype. For specific treatment regimen including sofosbuvir, the IFNL4 variant still influences treatment outcomes although the SVR remains relatively high for all IFNL4 genotypes. For example, a trial for the treatment-naïve genotype 1, 4, 5, 6 patients treated with 12 weeks of SOF+PEG-IFN+R (NEUTRINO study),⁴ the SVR rates were 98% in individuals with C/C allele and 87% in individuals with non-C/C allele. The individuals in this study had genotype 1 or 4 HCV infection and received SOF+PEG-IFN+R. The frequency of the rs12979860 favor-

able C/C alleles varies broadly across different populations, allele frequency was nearly 0.9 in East Asians, followed by Caucasians (0.63) and Hispanics (0.55), and is the least common in patients of African origin (0.39). In Korea, this C/C polymorphism was found in 81-88% of the patients.^{11,17}

In genotype 2, clinical significance of IFNL4 gene polymorphism is still uncertain. In FISSION study including genotype 2, 3 treated with SOF+R,⁴ the SVR rate was 69% in individuals with C/C allele and 66% in individuals with non-C/C allele. In POSITRON study including IFN-ineligible genotype 2 patients treated with SOF+R,⁶ the SVR rate was 76% in individuals with C/C allele and 79% in individuals with non-C/C allele. In a Japanese study,¹³ SVR rate were 98% in subjects with C/C allele and 94% in non-CC alleles. In a Korean study,¹¹ SVR rate were 97% in subjects with C/C allele and 96% in non-CC alleles.

Since there are too many DAA treatment options and those SVR rates are excellent, there will be low possibility to prove clinical significance of SOF+R treatment in future trials. Nevertheless, because of the aforementioned reasons including acceptable safety profiles, excellent SVR rate, and possibility of economic advantage, the SOF+R may be the one of the best first line options for genotype 2 chronic hepatitis C patients who cannot receive other DAAs in Korea.

Conflicts of Interest

The author has no conflicts to disclose.

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