

Once-daily simeprevir in combination with pegylated-interferon and ribavirin: a new horizon in the era of direct-acting antiviral agent therapy for chronic hepatitis C

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Received: 7 December 2013 / Accepted: 10 December 2013 / Published online: 21 December 2013
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Hepatitis C virus (HCV) is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC), and it is estimated that infected individuals total 185 million people worldwide. In Japan, around 2 million are infected with HCV, and more than 20 thousand die from HCV-induced HCC annually. Though viral eradication with antiviral therapies is the most important and effective choice for decreasing HCC-related deaths induced by HCV, complete viral eradication has been quite difficult till recently, especially in patients with genotype-1 HCV infection because of the low response rate to interferon (IFN)-based therapy [1, 2].

In this background, development of novel direct-acting antiviral agents (DAAs) specific for HCV was truly a revolutionary event. In 2011, two first-generation NS3 protease inhibitors (PIs), telaprevir and boceprevir, were firstly approved among all the DAAs for clinical use in USA and Europe for genotype-1 HCV in combination with pegylated-interferon and ribavirin (PR), while telaprevir was approved in Japan in the same 2011 period. As expected, a regimen including telaprevir in combination with pegylated-interferon and ribavirin dramatically improved the sustained viral response (SVR) rate to as high as 80 % in genotype-1 HCV infection. On the other hand, telaprevir has several undesirable problems. Among all, adverse events (AEs) of anemia and skin rash are serious problems of telaprevir, and Grade 3/4 skin disorders,

including Stevens–Johnson syndrome and drug rashes with eosinophilia and systemic symptoms, as well as Grade 3 anemia (<8.0 g/dL), might occur [3, 4]. Moreover, cumbersome frequent dosing three times a day (every 7–9 h) could induce poor medication adherence. Under the circumstances, it has been quite stressful for patients as well as clinicians to introduce and monitor this telaprevir-based regimen.

Simeprevir (SMV, TMC435) is classified as a second-generation PI with the macrocyclic structure having an advantage in the binding affinity and specificity for NS3 protease compared to the first-generation PI with the linear structure. Due to the difference in the structure, the drug-resistance profile is somewhat different from that of telaprevir. Though simeprevir shows cross-resistance with telaprevir at amino acid positions of 155 and 156, most of the resistant mutation occurs at the simeprevir-specific amino acid position of 168 [5]. Though simeprevir is effective in all viral genotypes (genotype 1–6), it has the strongest antiviral activity for genotype-1a and -1b HCV infection. In particular, low AE rate and its patient-friendly once-daily dosing are the important characters of simeprevir aside from its strong antiviral activity. In the international phase II trials of simeprevir in combination with PegIFN α -2a/RBV for treatment-naïve (PILLAR study) [6] and treatment-experienced patients (ASPIRE study) [7] for HCV genotype 1-infected patients, it was demonstrated that simeprevir was generally well tolerated and had a pharmacokinetic profile supporting once-a-day (QD) dosing resulting in high virologic response rates.

In this issue of the *Journal of Gastroenterology*, Hayashi et al. [8] reported the important results of the phase II Dose and duration Ranging study of Antiviral agent TMC435 in Genotype One HCV treatment-Naïve patients (DRAGON study; TMC435-C215) evaluating once-daily simeprevir

This comment refers to the article available at doi:[10.1007/s00535-013-0875-1](https://doi.org/10.1007/s00535-013-0875-1).

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with pegylated-interferon and ribavirin therapy for treatment-naïve, high viral-loaded hepatitis C genotype 1-infected patients in Japan. Due to the result of previous phase I study that simeprevir plasma concentration was higher in Japanese healthy volunteers compared with Caucasian volunteers, simeprevir doses of 50/100 mg QD were selected for this study, while simeprevir doses of 150 mg QD were selected in western countries [9]. Through investigating five treatment groups (SMV12/PR24 50 mg, SMV12/PR24 100 mg, SMV24/PR24 50 mg, SMV24/PR24 100 mg, and PR48), it was disclosed that simeprevir-combined groups all achieved high SVR rate (77–92 % compared to 46 % for PR). As to the AEs, simeprevir was well tolerated, and the incidence of anemia and skin rash were similar in their frequency and their grade between all the SMV groups and the PR group. Due to low AEs, therapy discontinuation rate and ribavirin dose reduction was also similar in the SMV groups and the PR group. While an AE of bilirubin elevation was specific to simeprevir, and it reached to grade 3 (2.6–5.0 mg/dL) to 4 (>5.0 mg/dL) in four patients (5 %) leading to the discontinuation of simeprevir in these individuals, the bilirubin level returned to baseline after the end of simeprevir in those patients. Since bilirubin elevation is considered to result from the blockade of bilirubin clearance-associated OATP1B1 and MRP transporters by simeprevir [10], it is considered that the bilirubin elevation by simeprevir does not reflect deterioration of liver function.

Following the results of this phase II DRAGON study, treatment dosage of simeprevir was determined as 100 mg QD in Japan, and successive phase III CONCERTO studies for simeprevir/pegylated-interferon/ribavirin therapy have been conducted (CONCERTO-1 for treatment-naïve, -2 for previous null responder, -3 for previous relapser, and -4 for naïve, null responder and relapser). After the completion of those CONCERTO studies with favorable outcomes for simeprevir-based regimens, once-daily simeprevir with pegylated-interferon and ribavirin therapy for high viral-loaded hepatitis C genotype 1-infected patients was just recently approved for clinical use in Japan.

Considering the history of HCV therapy, this new therapy of once-daily simeprevir with pegylated-interferon and ribavirin therapy is ideal in its high efficacy and low AEs. Of course, it is true that DAA combination therapies without IFN (IFN-free therapies) would appear in the near future, and that these IFN-free therapies are advantageous in that they are free from IFN-related AEs. However, in terms of DAA-resistant viral mutants, it is considered that

these mutant HCVs generally have low replication fitness, and are sensitive to IFN. Therefore, it is speculated that IFN-based DAA therapies compared to IFN-free DAA therapies are safer in preventing the development of multidrug resistant HCVs.

Taken together, the new regimen of once-daily simeprevir with pegylated-interferon and ribavirin therapy would surely be an important milestone in the therapy for high viral-loaded hepatitis C genotype-1 infected patients in the era of DAA therapy.

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