

## Emerging Therapies for Hepatitis C

Do Young Kim, Sang Hoon Ahn, and Kwang-Hyub Han

Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

The combination of pegylated interferon (PEG-IFN) and ribavirin (RBV), the current therapy for hepatitis C virus (HCV) infection, has saved the lives of many HCV-infected patients. Direct-acting antivirals (DAAs) target several sites of HCV nonstructural proteins, resulting in the cessation of viral replication. The first NS3/4A protease inhibitors consisted of boceprevir and telaprevir, which have shown superior efficacy against genotype 1 HCV infection when combined with PEG-IFN/RBV compared with the standard therapy in both treatment-naïve and -experienced patients. Simeprevir, faldaprevir, and asunaprevir are second-wave, first-generation NS3/4A inhibitors that have already been or will soon be approved. Second-generation protease inhibitors are in clinical trials. Daclatasvir is the first approved DAA belonging to the class of NS5A replication complex inhibitors. The potency of daclatasvir is very high, and this drug is an important and essential component of combination regimens for all genotypes. Sofosbuvir, the first approved NS5B polymerase inhibitor, is characterized by high potency and genetic barriers to resistance. Sofosbuvir combined with RBV achieved an interferon-free regimen in genotype 2 or 3 patients with a reduced treatment duration. It can also be used in combination with PEG-IFN/RBV in genotype 1 patients for 12 weeks. DAAs have provided new hope for curing HCV infections with a short treatment duration and acceptable adverse events.

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**Key Words:** Hepatitis C; Direct acting antiviral; Pegylated interferon; Ribavirin

### INTRODUCTION

Hepatitis C virus (HCV) infection globally presents a serious health burden. Approximately 3% of the population is known to be infected with HCV worldwide and the prevalence differs

even among Asia-Pacific countries, from 1% to 2% in most areas to 15.6% in Mongolia.<sup>1-3</sup> Although there is a controversy on the natural course of chronic hepatitis C (CHC),<sup>4</sup> a third of those infected with HCV are estimated to develop cirrhosis within 20 years.<sup>5</sup> Data have shown that eradication of HCV by antiviral treatment could prevent histological deterioration and result in improvement of liver histology,<sup>6</sup> as well as reduction in liver-related morbidity and mortality.<sup>7</sup> The combination of pegylated interferon- $\alpha$  (PEG-IFN) and ribavirin (RBV) has been a standard of care for the management of CHC and this regimen significantly contributed to improvement of long-term clinical outcomes of treated patients. Nevertheless, the rate of treatment success defined by sustained virologic response (SVR) is just 40% to 50% in genotype 1 infection.<sup>8</sup> Because of the adverse events and discomforts by administration of PEG-IFN and RBV, frequent dose reduction and discontinuation resulting in intolerance and treatment failure are also disadvantages of the current therapy for hepatitis C. Other shortcomings of PEG-IFN/RBV therapy are that HCV eradication is hardly expected in patients with high baseline viral loads, older age, advanced fibrosis and high body mass index.<sup>9</sup>

In HCV treatment, a substantial progress has been made after development of the first two NS3/4A oral protease inhibitors, boceprevir (BOC) and telaprevir (TVR), which were recently approved for use in combination with PEG-IFN/RBV. The so-called direct-acting antiviral (DAA) opened a new era for the possibility of interferon-free therapy, lower pill-burden, increased treatment success rate as well as reduced duration of therapy. Multiple, concomitant clinical trials of new DAAs being conducted represent a fast and extensive research for anti-HCV treatment. Besides the HCV proteins such as NS3/4A, NS5A, NS5B as targets of therapy, therapeutic vaccines, drugs targeting host protein, other kinds of interferon are also under development. In this review, we aim to summarize the advantages and limitations of the currently available DAAs, new DAAs in clinical trials.

Correspondence to: Kwang-Hyub Han

Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea

Tel: +82-2-2228-1992, Fax: +82-2-2393-6884, E-mail: gihkhys@yuhs.ac

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## CLASSIFICATION OF DAAs

The targets of currently approved or in development are related with HCV replication, specifically translation and polyprotein processing (NS3/4A), HCV genome replication (NS5B polymerase and NS5A), and viral assembly (NS5A).<sup>10</sup> Inhibition of NS3 (serine protease) and its cofactor, NS4A, results in blocking proteolytic maturation of a large portion of the nonstructural region of the HCV polyprotein, NS3 to NS5B. BOC and TVR are the first NS3/4A protease inhibitors approved for the treatment of genotype 1 infection. A number of other protease inhibitors, which have been developed and in phase II or III clinical trials, are classified as “first-generation” and “second-generation” according to degree of genetic barrier to resistant HCV and genotype coverage. The first-generation protease inhibitors include BOC, TVR, simeprevir (TMC-435), faldaprevir (BI201335), vaniprevir (MK-7009), and asunaprevir (BMS-650032). The second-generation protease inhibitors, characterized by potent activity against pan-genotypes and high genetic barrier to resistance, include MK-5172 and ACH-2684 in phase II clinical trial. NS5A is a dimeric protein required for HCV RNA replication and virion assembly.<sup>11</sup> NS5A inhibitors have potent antiviral activity, but the genetic barrier to resistance is low. Daclatasvir (BMS-790052), GS-5885, ABT-267, PPI-668 are included in NS5A

inhibitors. The NS5B, RNA-dependent RNA polymerase (RdRp), is an attractive target for anti-HCV therapy since this enzyme is directly responsible for the HCV RNA genome synthesis. As RNA chain terminators, NS5B polymerase inhibitors are classified into nucleos(t)ide inhibitors (NIs) and nonnucleos(t)ide inhibitors (NNIs) according to the structures. NIs have potent antiviral activity across all HCV genotypes and have high genetic barrier to resistance. Sofosbuvir (SOF) (GS-7977), which has recently been approved as “interferon-free” drug by Food and Drug Administration (FDA) in the United States, is the most advanced NI. Mericitabine (RG7128) and VX-135 are other NIs in phase II clinical trials. Owing to binding to less conserved sites on NS5B, NNIs do not have antiviral activity against pan-genomic HCV and have low genetic barrier to resistance. Several NNIs including ABT-333, ABT-072, BI207127 are being evaluated in combination with other antiviral agents. Table 1 summarizes the structural characteristics, potency and genetic barrier of each DAA approved or in clinical trials.

## NS3/4A INHIBITORS

### 1. Boceprevir

BOC is now an approved NS3/4A inhibitor for the treatment of genotype 1 HCV infection at a dose of 800 mg, 3 times in

**Table 1.** Classes and Characteristics of Direct-Acting Antivirals

Class	Structural, functional characteristics	Potency	Genetic barrier to resistance	Compound	Current status	
NS3/4A protease inhibitors	Inhibiting proteolytic maturation of HCV polyprotein	High in G1 Low in G2/3	Low to medium	Boceprevir	Approved	
				Telaprevir	Approved	
				Simeprevir (TMC-435)	Approved	
				Faldaprevir (BI201335)	Phase III	
	Second-generation	Covalent linear inhibitors Noncovalent linear inhibitors Macrocyclic inhibitors	High in all G	Medium	Asunaprevir (BMC-650032)	Phase III
					Danoprevir (RG7227)	Phase II
					Vaniprevir (MK-7009)	Phase III
					MK-5172	Phase II
					ACH-2684	Phase II
NS5A inhibitors	Biding to domain I of NS5A, resulting in the suppression of RNA synthesis	High	Low to medium	Daclatasvir	Phase III	
				GS-5885	Phase III	
				ABT-267	Phase III	
				PPI-668	Phase II	
NS5B polymerase inhibitors	Mimics of natural polymerase substrates. Incorporated in the RNA leading to chain termination	High in all G	Medium to high	Sofosbuvir	Approved	
				Mericitabine (RG7128)	Phase II	
				VX-135	Phase II	
	Nonnucleos(t)ide inhibitors	Binding to the surface of NS5B enzyme	Medium to High	Low	ABT-333	Phase III
					BI207127	Phase III
					ABT-072	Phase II

HCV, hepatitis C virus.

combination with PEG-IFN/RBV.<sup>12</sup> In a randomized, multicenter phase II trial (SPRINT-1), BOC combined with PEG-IFN/RBV for 24 weeks after lead-in PEG-IFN/RBV for 4 weeks in genotype 1 achieved 56% of SVR rates, which were significantly higher than 38% in control group (PEG-IFN/RBV for 48 weeks). When duration of triple therapy was extended to 44 weeks after 4-week of PEG-IFN/RBV lead-in therapy, the SVR rates increased to 75%. Interestingly, virologic response during the lead-in period guided the duration of triple therapy; patients achieving less than 1.5 log<sub>10</sub> reduction in viral levels after lead-in could benefit from duration of a total 48 weeks, while those with greater than 1.5 log<sub>10</sub> reduction had similar SVR rate regardless of treatment duration of 28 weeks or 48 weeks.<sup>13</sup> The most common adverse event of BOC was found to be anemia, which appeared to contribute to higher discontinuation rate of BOC-containing antiviral treatment (9% to 19%) compared with control group (8%). A phase III trial of BOC (SPRINT-2) including 938 nonblack patients highlighted the importance of response-guided therapy (RGT). The rates of SVR in patient who received 24 weeks of triple therapy after 4 weeks of lead-in period, and achieved undetectable HCV RNA at week 8 through week 24, was 97%, which was comparable with 96% in patients who received 44 weeks of triple therapy and a total of 48 weeks of therapy. Additional PEG-IFN/RBV after 24 weeks of triple therapy was not helpful in patients in whom HCV RNA levels were still detectable at week 8, since there was no difference of SVR rate (74%) between patients who received PEG-IFN/RBV for 20 weeks more and those who did not.<sup>14</sup> BOC has been shown to increase SVR rates in retreatment for genotype 1 HCV-infected patients who failed previous PEG-IFN/RBV therapy. In a randomized trial (RESPOND-2), BOC for 32 weeks or 44 weeks in combination with PEG-IFN/RBV after 4 weeks of lead-in period of PEG-IFN/RBV resulted in the SVR rates of 59% and 66%, respectively, which were significantly higher than 21% in 48 weeks of PEG-IFN/RBV (control).<sup>15</sup> Anemia was also more common adverse event in BOC-based treatment than in the control. Retreatments with BOC-based regimen was more effective in patients who showed relapse or partial response to previous standard therapy than those who showed prior null response. In a study of 168 patients in control arms of BOC phase II/III trials who did not achieve treatment success, SVR rates after retreatment with triple therapy were 41%, 67%, and 96% in prior null responders, partial responders, and relapsers, respectively.<sup>16</sup>

Advanced fibrosis or cirrhosis related to HCV infection is the most urgent indication of antiviral therapy since the risk of hepatic decompensation or development of hepatocellular carcinoma is high. Furthermore, several studies have reported that achievement of SVR in patients with compensated cirrhosis could prevent disease progression and lead to improved survival.<sup>17,18</sup> The number of cirrhotic patients in clinical trials is limited, thus, the efficacy or safety of BOC is uncertain in these patients. In a study of 178 genotype 1 HCV patients with

Metavir F3 or F4 who participated in the two pivotal BOC trials (SPRINT-2 and RESPOND-2),<sup>14,15</sup> the overall SVR rates was 11% to 33% in F3 patients and 10% to 14% in F4 patients who received BOC-based response guided therapy or BOC/PEG-IFN/RBV for 44 weeks after lead-in period of 4 weeks.<sup>19</sup>

The factors that predict response to BOC/PEG-IFN/RBV were sought by analyzing the data from SPRINT-2 and RESPOND-2 trials.<sup>14,15</sup> In naive genotype 1 patients, low viral load ( $\leq 400,000$  IU/mL), IL-28B rs12979860 CC genotype, absence of cirrhosis, HCV subtype 1b, and nonblack were the independent baseline factors predicting SVR. Among these, IL-28B polymorphism was the strongest factor. On the other hand, in treatment-experienced patients, only previous relapse (vs nonresponse) was the significant factor associated with prediction of response. Moreover, decline of HCV RNA  $\geq 1$  log<sub>10</sub> at week 4 was a strong predictor of achievement of SVR, and this was the on-treatment factor that was stronger than IL-28B polymorphism in predicting response to BOC-containing regimen.<sup>20</sup>

Practically, the product labels indicate that 4-week lead-in phase of PEG-IFN/RBV should precede the administration of BOC. When the patient is naive, noncirrhotic and has genotype 1 infection, a response-guided therapy is recommended to determine the duration of triple therapy (24 or 32 weeks), depending on the response at specific time points; if HCV RNA remained detectable at any visit from week 8 up to but not including week 24, triple therapy should be continued until 32 weeks (after 4-week lead-in), and additional PEG-IFN and RBV should be administered for 12 weeks (total duration, 48 weeks). For the previous null responders to PEG-IFN/RBV or cirrhotic patients, 4-week lead-in period followed by 44 weeks of triple therapy is recommended. All treatments should be discontinued if HCV RNA levels  $\geq 100$  IU/mL at week 12 or detectable ( $\geq 10$  to 15 IU/mL) at week 24.<sup>21</sup> Currently, the recommendations by the FDA in the United States and European Medicines Agency (EMA) differ in terms of BOC use for the treatment-experienced patients with genotype 1.<sup>22</sup> The EMA still recommend that all treatment-experienced patients continue to receive fixed, 48 weeks therapy rather than response-guided therapy.

## 2. Telaprevir

TVR, another first-generation NS3/4A inhibitor, demonstrated higher SVR rates when used in combination with PEG-IFN/RBV compared to standard therapy. In a clinical trial of genotype 1 patients, TVR was administered together with PEG-IFN/RBV for the initial 12 weeks. The SVR rates of patients who received 24 weeks and 48 weeks of PEG-IFN/RBV were 61% and 67%, respectively, which were significantly higher than 41% in those receiving PEG-IFN/RBV alone for 48 weeks.<sup>23</sup> The most frequent adverse event associated with TVR was rash which resulted in higher discontinuation of therapy in TVR-based regimen than in PEG-IFN/RBV treatment (21% vs 11%). In a subsequent phase III trial (ADVANCE), patients with genotype 1 received

TVR and PEG-IFN/RBV for 8 or 12 weeks followed by PEG-IFN/RBV in a response-guided manner. If extended rapid virologic response (eRVR), which was defined as undetectable HCV RNA at week 4 and 12, was achieved, treatment was stopped at week 24 whereas patient who did not achieve eRVR continued antiviral therapy until week 48. Overall, the SVR rates were 69% and 75% in those who received TVR for 8 weeks and 12 weeks, which were significantly higher than 44% in the control (PEG-IFN/RBV alone). Of note is that the SVR rates of those who achieved eRVR in 8-week and 12-week TVR were 89% and 83%, respectively.<sup>24</sup>

Retreatment with TVR-containing regimen exhibited higher treatment success rates in genotype 1 patients who did not achieve SVR with previous PEG-IFN/RBV therapy. In those patients who were given 12 weeks of TVR and 24 weeks of PEG-IFN/RBV, the SVR rates were 51%. Similarly, patients who received 24 weeks of TVR and 48 weeks of PEG-IFN/RBV showed SVR rates of 53%, which were significantly higher than 14% in those who were retreated with only PEG-IFN/RBV.<sup>25</sup> The most common adverse event associated with TVR was rash, occurring in 51% of patients. In another phase III trial (REALIZE), patients were randomly assigned to one of three groups; triple therapy for 12 weeks followed by PEG-IFN/RBV for 36 weeks, lead-in therapy with PEG-IFN/RBV for 4 weeks followed by triple therapy for 12 weeks and PEG-IFN/RBV for 32 weeks, standard-of-care of 48 weeks of PEG-IFN/RBV alone for 48 weeks (control). The SVR rates were 64% and 66% in two TVR-containing regimens, which were significantly higher than 17% in the control group.<sup>26</sup> As in BOC trial, TVR-based triple therapy was most effective in patients who showed relapse to prior PEG-IFN/RBV treatment, compared to partial or null response to the previous therapy. The SVR rates in the first two arms in REALIZE study were 83% and 88%, respectively, while the rates were 59% and 54% in partial responders, 29% and 33% in null responders.<sup>26</sup>

Regarding safety of triple therapy in cirrhotic patients, European multicenter study of 674 genotype 1, treatment-experienced patients who had been recruited in an early access program, which enabled eligible patients to receive BOC or TVR before marketing authorization, showed a high incidence of serious adverse events (40%), death and severe complications. The rate of erythropoietin or transfusion use reached 50.7% and 12.1%. The independent risk factors associated with side effects were found to be low platelet count ( $\leq 100,000/\text{mm}^3$ ) and serum albumin less than 3.5 g/dL.<sup>27</sup>

The recommendation of TVR use in real clinical practice according to FDA is that 12-week administration of TVR and PEG-IFN/RBV should be followed by PEG-IFN/RBV alone through week 24 or 48, as determined by attainment of eRVR in treatment-naïve patients or in previous relapsers. The treatment duration for cirrhotic patients and partial (or null) responders to previous PEG-IFN/RBV might be a fixed, total 48 weeks (36 weeks of PEG-IFN/RBV following 12-week of triple therapy).<sup>22</sup>

### 3. Simeprevir

At the time this article is written, the available literature published which reports the efficacy and safety of simeprevir (SMV), a second-wave NS3/4A protease inhibitor, in genotype 1 treatment-naïve patients is a result from a phase IIb trial.<sup>28</sup> Patients in SMV arms were randomly assigned to once-daily SMV (75 or 150 mg) for 12 or 24 weeks, plus PEG-IFN and RBV. The control group received 48 weeks of PEG-IFN and RBV. The response-guided therapy was applied; if HCV RNA  $<25$  IU/mL at week 4 and undetectable at weeks 12, 16, 20, all therapy completed at week 24 in SMV arms. If these criteria of RGT were not met, the total duration of treatment was 48 weeks. SVR rates in SMV arms ranged 74.7% to 86.1% which were significantly higher 64.9% in the control group, except for the comparison between SMV 75 mg for 24 weeks and control. Interestingly, 79.2% to 86.1% of SMV-treated patients met the RGT criteria, and completed treatment by week 24. The SVR rates of those who shortened treatment duration according to RGT were 85.2% to 95.6%. Serious adverse events occurred with similar frequency between SMV-arms and control. A mild, reversible hyperbilirubinemia without concomitant increase of aminotransferase was observed in SMV-treated patients.

The results of subsequent phase III trials (QUEST-1, QUEST-2) are going to be published soon. In these pivotal trials, patients in treatment groups were given SMV 150 mg daily plus PEG-IFN/RBV for 12 weeks, followed by PEG-IFN/RBV alone for either 12 or 36 weeks according to the RGT criteria.<sup>29,30</sup> The control group was given placebo for 12 weeks combined with PEG-IFN and RBV for 48 weeks. Since the trial design of QUEST-1 and -2 was basically identical, two studies were pooled. The SVR rates measured at 12 weeks posttreatment in SMV arms were 80%, which were significantly higher than 50% in the control arm. It might be highlighted that 85% of patients in QUEST-1 and 91.4% in QUEST-2 trial could shorten the treatment duration to 24 weeks according to RGT. The SVR rates in those who met RGT criteria were 91% and 86% in each trial.

Retreatment with SMV-based triple regimen increased the SVR rates in comparison with PEG-IFN and RBV. In a phase IIb trial, patients with treatment-failure to prior therapy were randomly assigned to SMV (100 or 150 mg, once daily) for 12, 24, or 48 weeks plus PEG-IFN and RBV for 48 weeks.<sup>31</sup> The control group was given PEG-IFN and RBV alone for 48 weeks. The rates of SVR were significantly higher in SMV-arms compared to control irrespective of prior response; overall 61%-80% versus 23%; 38%-59% versus 19% in null responders; 48%-86% versus 9% in partial responders; 77%-89% versus 37% in relapsers. The incidence of adverse events occurred with similar frequency between SMV-arms and control group. SMV 150 mg tended to show higher SVR rates compared to 100 mg. The design of randomized, controlled phase III trial of SMV in combination with PEG-IFN and RBV for retreatment for relapsers

was identical to QUEST-1 and -2. The rates of SVR measured at week 12 after completion of therapy were 79% in SMV-arm and 36% in the control. Most of the SMV-treated patients (92.7%) were eligible to shorten duration of therapy to 24 weeks and their SVR rates were 83%.<sup>32</sup>

The first approval of SMV was made in Japan in November 2013. U.S. FDA also approved SMV for the treatment of genotype 1 CHC, in combination with PEG-IFN and RBV in December 2013.

#### 4. Faldaprevir

Faldaprevir (FDV), another second-wave NS3/4A protease inhibitor, has an advantage of once-daily dosing like simeprevir. In a global phase IIb trial, a total of 429 treatment-naïve genotype 1 patients were randomized to 24 weeks of PEG-IFN/RBV in combination of FDV 120 mg with 3 days of PEG-IFN/RBV lead-in, FDV 240 mg with lead-in, or FDV 240 mg without lead-in.<sup>33</sup> The control group was given 48 weeks of PEG-IFN and RBV. Regardless of lead-in period, all patients in FDV 240 mg were again randomized either to stop treatment at week 24 or to continue treatment until week 48 according to the presence of maintenance of rapid virologic response (mRVR) defined by HCV RNA <25 IU/mL at week 4 and undetectable HCV RNA at week 8 to 20. The SVR rates were the highest (84%) in group of FDV 240 mg without lead-in period. Furthermore, the SVR rates of patients who achieved mRVR were 92%. Unconjugated hyperbilirubinemia, rash, and photosensitivity were found to be adverse events associated with administration of FDV.

The results of two large multicenter, randomized, phase III trials of FDV (STARTVerso 1 and 2) were recently presented.<sup>34,35</sup> A total of 84% of FDV-treated patients achieved mRVR and could shorten treatment duration to 24 weeks. Among those who achieved mRVR, overall SVR rates were 83%.

The efficacy and safety of FDV without interferon has been evaluated in a phase IIb trial, where a total of 362 genotype 1 patients were randomized to several groups of different treatment duration. The SVR rates at 12 weeks after completion of therapy was the highest (69%) in patients who were given FDV 120 mg once daily, deleobuvir, a nonnucleoside polymerase inhibitor, 600 mg twice daily, and RBV for 28 weeks.<sup>36</sup> This result seems to be unsatisfactory compared with other interferon-free regimen, thus the combination of FDV and deleobuvir would not be further investigated in genotype 1 patients.

#### 5. Asunaprevir

Asunaprevir (ASV), a selective NS3 protease inhibitor, showed a potent antiviral activity when combined with PEG-IFN and RBV, against genotype 1 HCV. In a phase IIa study, the SVR rates in patients who received asunaprevir 600 mg once daily and PEG-IFN/RBV for 48 weeks were 92%. The dose of ASV was determined to be optimal at 200 mg twice daily since 600 mg of asunaprevir had a greater frequency of transaminase

elevations although ASV 200 mg twice daily combined with PEG-IFN/RBV had lower SVR rates, 83%.<sup>37</sup> A promising result has been reported in a Japanese phase IIa study, where 21 null responders to PEG-IFN/RBV and 22 patients intolerant to or ineligible for PEG-IFN/RBV were given ASV and daclatasvir (DCV), a NS5A inhibitor, for 24 weeks. The overall SVR rates assessed at week 12 and 24 after completion of dual therapy were 76.7%. Diarrhea, nasopharyngitis, and headache were the most common adverse events and discontinuation of therapy occurred in two patients due to hyperbilirubinemia and transaminase elevation.<sup>38</sup> In another Western phase IIa study, dual therapy with ASV and DCV or triple therapy with ASV, DCV, and RBV was not effective for genotype 1a patients who experienced null response to prior PEG-IFN/RBV therapy. On the contrary, quadruple therapy (ASV, DCV, and PEG-IFN/RBV) was effective nearly all genotype 1a patients with prior null response.<sup>39</sup>

All-oral, interferon-free regimen including ASV, DCV has been evaluated in a phase IIa study. A total of 66 treatment-naïve genotype 1 noncirrhotic CHC patients were randomly assigned to ASV (200 mg, twice daily), DCV (60 mg, once daily) and BMS-791325 (a nonnucleoside NS5B inhibitor) for 12 or 24 weeks. The SVR rates at week 12 posttreatment were 92% and there was no difference of virologic response between 12 and 24 weeks of treatment. The most frequent adverse events were headache, asthenia, and gastrointestinal symptoms.<sup>40</sup>

### NS5A INHIBITORS

#### 1. Daclatasvir

DCV is the first of DAA targeting against hepatitis C virus NS5A showing a very potent antiviral effect on several HCV genotypes. The overall adverse event profile is acceptable and its pharmacokinetics allow once-daily oral administration. Due to a relatively low genetic barrier of DCV, combination regimen including DCV and other NS3/4A, PEG-IFN/RBV, or NS5B drugs is recommended for the treatment of hepatitis C.<sup>41</sup>

The efficacy and safety of DCV in combination with PEG-IFN/RBV were evaluated in treatment-naïve genotype 1 patients. The patients receiving DCV 60 mg and PEG-IFN/RBV for 24 or 48 weeks showed 90.0% of SVR rates, which were higher than 66.7% in DCV 10 mg and PEG-IFN/RBV. The adverse events in group receiving DCV plus PEG-IFN/RBV were similar to those who were given PEG-IFN/RBV alone.<sup>42</sup>

The benefit of DCV is that viral resistance profile induced by DCV is not overlapped with other DAAs, which would suggest the most synergistic antiviral effect when combined with other kind of DAAs by suppressing the emergence of all possible multiple resistant variants.<sup>43</sup> The data of efficacy and safety of DCV and other DAAs will be presented in the followings.

#### 2. ABT-267

ABT-267 is a potent NS5A inhibitor and was recently report-

ed to have a promising efficacy in difficult-to-treat genotype 1 patients when combined with other DAAs. In a phase IIb trial, a total of 133 who had not had a response to prior standard therapy were randomly assigned to ABT-450 (protease inhibitor) with ritonavir (ABT-450/r), combined with ABT-267 or ABT-333 (NNI NS5B inhibitor) or both for various treatment durations. Interestingly, the SVR rates across all the groups, ranged 89% to 95%. Serious adverse events rarely occurred and the most common adverse events were fatigue, headache, nausea, and insomnia.<sup>44</sup>

## NS5B INHIBITORS

### 1. Sofosbuvir

SOF, a nucleotide analogue NS5B polymerase inhibitor, received its first global approval for the treatment of chronic hepatitis C by the U.S. FDA in December 2013. Monotherapy of SOF is not recommended for treatment of CHC. The dose of SOF is 400 mg once daily, taken with or without food. According to package insert, SOF can be administered for 12 weeks in combination with PEG-IFN/RBV in HCV genotype 1 or 4 infection; SOF and RBV for 24 weeks is an alternative in genotype 1 patients who are ineligible to receive an interferon-based treatment. In genotype 2 and 3 infection, interferon-free regimen of SOF and RBV for 12 weeks and 24 weeks, respectively, is an option.<sup>45</sup>

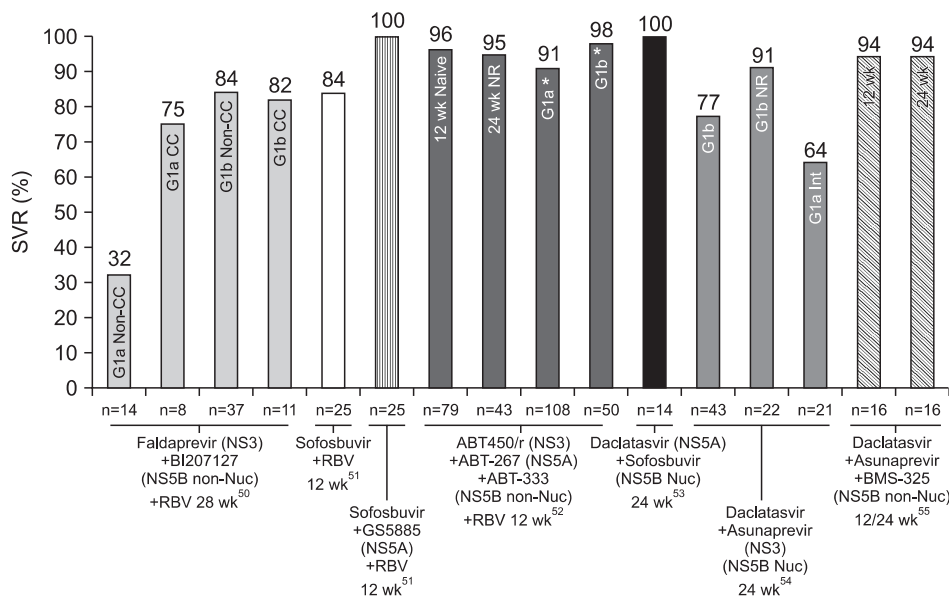
Actually, SOF has opened the first window for the era of “interferon-free” treatment of hepatitis C. A lot of clinical trials of SOF are now ongoing to optimize the regimen and treatment duration for each HCV genotype. The approved, reduced treatment duration (12 weeks) of PEG-IFN/RBV in combination with SOF is based on the results of phase III clinical trial called NEUTRINO where a total of 327 patients with genotype 1, 4, 5, or 6

infection were recruited. The overall SVR rates were 91%, and genotype-specific SVR rates were 90% in genotype 1 and 96% in genotype 4.<sup>46</sup>

A randomized, open-label, phase II study (ATOMIC trial) showed that 12 weeks of SOF plus PEG-IFN/RBV was comparable to 24 weeks of triple regimen. The SVR rates of patients who were given 12 weeks and 24 weeks of SOF/PEG-IFN/RBV were the same (89%). Patients who received SOF alone or SOF plus RBV for additional 12 weeks after triple regimen for 12 weeks showed SVR rates of 87%.<sup>47</sup>

Fission trial has evaluated the efficacy of SOF plus RBV (interferon-free regimen) for 12 weeks compared with standard therapy in genotype 2 or 3 infection. Between two groups, the SVR assessed at week 12 after completion of therapy was the same, 67%.<sup>46</sup> Another randomized, phase III study (POSITRON trial) of genotype 2 or 3 patients who had previously discontinued treatment with interferon due to adverse event or other reasons such as concomitant disease, unwillingness confirmed the efficacy of SOF plus RBV regimen. The SVR rates in these patients were 78% versus 0% in control group.<sup>48</sup>

As mentioned before, DCV has the potential benefit of synergistic antiviral effect when combined with other DAAs. Recently, data of a multicenter, open-label study of SOF plus DCV were reported. Among treatment-naïve or experienced patients with genotype 1, 2, or 3, various combinations of regimen (SOF plus DCV with or without RBV) and treatment duration (12 or 24 weeks) were examined. Surprisingly, 98% of 126 previously untreated patients and 98% of 41 previously failed to protease inhibitors achieved SVR at week 12 after completion of therapy. The SVR rates in genotype 2 and 3 patients were 92% and 89%, respectively. There was no pre-existing SOF resistance polymorphism or emergence at the end of therapy; however, NS5A-A30K polymorphism associated with DCV resistance was



**Fig. 1.** Sustained virologic response (SVR) rates in patients with genotype 1 hepatitis C virus (HCV) infection treated by all-oral, interferon-free regimens. Data were from different studies and are therefore not comparable among agents (different inclusion criteria, different treatment durations, assessment of SVR at different time points; week 12 or 24). In each study, the results from the treatment group with the highest SVR were reported. ‘CC’ indicates IL28B rs12979860 genotype CC, and ‘G’ indicates genotype. NR, nonresponse; Int, intolerant to pegylated interferon and ribavirin; Nuc, nucleos(t)ide inhibitor; RBV, ribavirin. \*Subtype analysis included combined data for 12- and 24-week regimens.

detected at baseline most frequently in genotype 2 patients.<sup>49</sup>

The adverse events related to SOF appear to be acceptable and manageable. Permanent discontinuation of therapy due to adverse events occurred in 1 and less than 1% of patients receiving SOF/RBV for 12 and 24 weeks, respectively, in 4% of placebo recipients, in 2% of SOF/PEG-IFN/RBV recipients and in 11% of PEG-IFN/RBV recipients.<sup>45</sup> The most frequent adverse events in patients who received SOF/RBV were fatigue, headache, nausea, insomnia, and pruritus.<sup>45</sup> With availability of SOF-based, interferon-free regimen for hepatitis C, patients on liver transplant waiting list or who have recurred HCV infection after transplantation are going to have more opportunities of receiving antiviral therapy without worsening liver function or graft rejection.

## 2. Perspectives of interferon-free regimen

Anti-HCV therapy is rapidly evolving and clinicians expect eradication of HCV on the earth within a few decades. Many global pharmaceutical industries are investing and developing new DAAs with improved efficacy and safety. The current interferon-free regimens approved or under clinical trials have substantially higher SVR rates compared with standard PEG-IFN/RBV treatment even in genotype 1 infection (Fig. 1).<sup>50-55</sup> Lower treatment duration, decreased pill burden and adverse events, no injection and higher SVR rates are attractive for physicians to consider change their practice from interferon-based therapy to oral regimens for HCV therapy. However, it is a major limitation that DAAs are very expensive. In developing countries, replacement of standard therapy by oral regimen would take time and depend on the expense of new drugs. In addition, it is still unknown whether these new therapy is effective for cirrhotic patients, the most-difficult-to treat population and long-term follow-up data will be needed to confirm excellent outcome of SVR. Development of DAAs obviously led to challenge and change in the paradigm of management for hepatitis C patients.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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