

New treatments for genotype 1 chronic hepatitis C – focus on simeprevir

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Abstract: Chronic hepatitis C virus (HCV) infection causes end-stage liver diseases and hepatocellular carcinoma. In the USA, Canada, and Japan, simeprevir – one of the second-generation HCV NS3/4A protease inhibitors – in combination with peginterferon α -2a or 2b plus ribavirin has recently been approved for HCV genotype 1-infected patients and is now used in daily clinical practice. This review summarizes the mechanism of action of simeprevir and the results of clinical trials of simeprevir and peginterferon plus ribavirin for HCV genotype 1 patients. In general, the simeprevir and peginterferon plus ribavirin treatment is highly effective and its adverse events are similar to those of peginterferon plus ribavirin only, the exception being milder, reversible jaundice. In the near future, the development of interferon-free regimens with simeprevir is expected. Careful attention should be paid to new results of clinical trials with simeprevir.

Keywords: hepatitis C virus, HCV NS3/4A protease inhibitor, hepatocellular carcinoma, TMC435

Introduction

Hepatitis C virus (HCV) is one of the major causes of chronic liver disease, hepatocellular carcinoma, and end-stage liver diseases in the USA, European countries, and Japan.^{1–3} In untreated patients with HCV, the steady progression of hepatic fibrosis is observed in many cases.⁴ Several studies indicated that once patients develop cirrhosis, hepatocellular carcinoma develops at approximately 1%–7% per year, and the rate is increasing.^{5,6} This clearly highlights the importance of HCV treatment.

HCV is a single-stranded RNA virus approximately 9.6 kb in length, and is of the *Hepacivirus* genus belonging to the *Flaviviridae* family.⁷ The HCV genome encodes at least ten proteins: four structural (core, E1, E2, and p7) and six non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B). Among them, HCV NS2 and NS3 are cysteine protease and serine protease, respectively. HCV genomes are translated into an open reading frame of approximately 3,011 amino acids in length. Then, viral and cellular proteases chop this protein into structural and non-structural proteins, which are important for HCV assembly and replication.⁷

Peginterferon plus ribavirin treatment leads to only 40%–50% sustained virologic response (SVR) in HCV genotype 1-infected patients but approximately 80% SVR in HCV genotype 2-infected patients.⁷ In 2011, boceprevir or telaprevir – both first-generation HCV NS3/4A protease inhibitors – in combination with peginterferon plus ribavirin became available for HCV genotype 1-infected patients.⁸ However, the treatment with HCV NS3/4A protease inhibitors is often associated with serious adverse events, despite achieving 70%–80% SVR in these patients.^{8–10}

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In the USA, Canada, and Japan, simeprevir – one of the second-generation HCV NS3/4A protease inhibitors – in combination with peginterferon plus ribavirin has recently been approved for HCV genotype 1-infected patients. This review focuses on and discusses simeprevir-including treatment for HCV genotype 1 infection.

Simeprevir (TMC435)

Simeprevir is an orally administered HCV NS3/4A protease inhibitor with a macrocyclic structure (Figure 1) and is one of the non-covalent inhibitors.¹¹ HCV NS3/4A protease inhibitors are divided into two classes: reversibly covalent and non-covalent. Boceprevir and telaprevir are linear peptidomimetic structures incorporating an α -ketoamide.¹² Simeprevir is a highly specific, potent HCV NS3/4A protease inhibitor, and biochemical assays have shown that HCV NS3/4A proteases of genotypes 1a and 1b, respectively, are inhibited with 0.5 nM and 0.4 nM of simeprevir.¹³ In genotypes except HCV genotype 3, simeprevir has been shown to be effective in vivo.^{14,15} This compound has synergistic effects with interferon- α and HCV NS5B inhibitor, and it has additive effects with ribavirin in HCV replicon cells.¹³ In rats, simeprevir was extensively distributed to the liver and intestinal tract, absolute bioavailability was 44% after a single oral administration, and compound concentrations were detected in both plasma and liver at 8 hours.¹³ It was reported in both in vivo and in vitro studies that amino acids V36M,

Q41R, F43S, T54S, Q80K/R/L, R155K, A156T/V, and D168N/A/V/E/H/T were resistance mutations to simeprevir.¹⁶ R155K and D168E are the common resistance mutations in HCV genotypes 1a and 1b, respectively,^{17–19} although further studies will be needed. To prevent the resistant variants from emerging, simeprevir should be used in combination with peginterferon plus ribavirin, or other classes of direct-acting antivirals against HCV.²⁰

Simeprevir with peginterferon plus ribavirin for treatment-naïve HCV genotype 1 patients

The Phase IIb, double-blind, placebo-controlled PILLAR trial (A Phase II Study of TMC435 in Combination with Peginterferon α -2a and Ribavirin in Patients Infected with Genotype 1 HCV Who Never Received Treatment; NCT00882908) examined the efficacy and safety of two different doses of simeprevir administered once daily (QD) for two different durations in combination with peginterferon plus ribavirin in treatment-naïve HCV genotype 1 patients.²¹ A total of 386 patients were randomly assigned to one of five groups (Figure 2): simeprevir (75 mg or 150 mg QD) for 12 or 24 weeks, or placebo, and peginterferon plus ribavirin. Patients in the simeprevir arms were treated for 24 or 48 weeks according to response-guided therapy (RGT) criteria. SVR rates, measured at 24 weeks after the end of treatment for each treatment group, are shown in Figure 2. SVR rates were 74.7%–86.1% in the simeprevir groups versus 64.9% in the placebo control group ($P < 0.05$).²¹ For patients treated with simeprevir 75 mg, the SVR rates were lower for genotype 1a (66.2%) than for genotype 1b (88.9%), although the SVR rates in genotype 1a (82.4%) and 1b (83.8%) patients were similar with simeprevir 150 mg.²¹ For the 332 patients with METAVIR scores of F0–F2, SVR rates were 81.7% with simeprevir 75 mg, 84.6% with simeprevir 150 mg, and 64.3% with placebo control. For the 53 patients with METAVIR scores of F3, SVR rates were 63.0% with simeprevir 75 mg, 75.0% with simeprevir 150 mg, and 71.4% with placebo control. Multiple regression analysis showed that treatment with simeprevir was associated with higher rates of SVR.²¹

Among simeprevir-treated patients infected with HCV genotype 1a, higher SVR rates were observed in patients without the Q80K polymorphism at baseline.²¹ It was reported that differences in the type of emerging mutations were observed between genotype 1a- (mainly emerging R155K alone or in combination with other mutations at NS3 positions 80 and/or 168) and 1b- (mainly D168V) infected patients.²¹

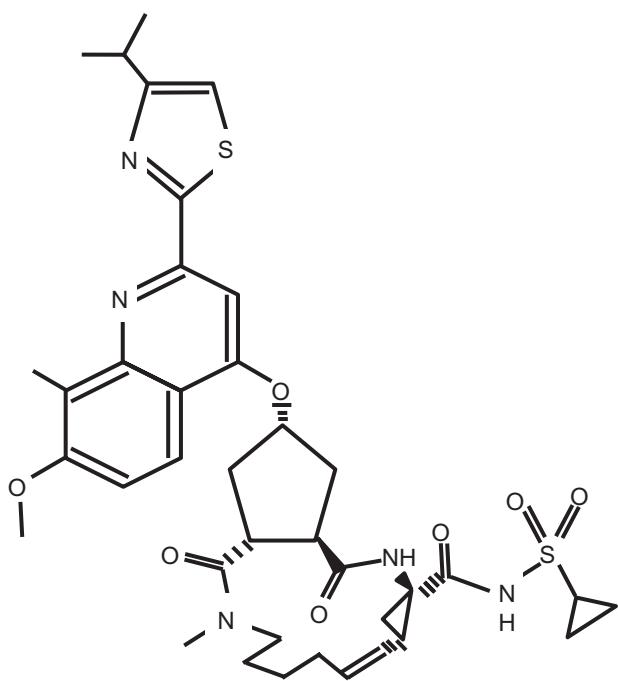


Figure 1 Structure of simeprevir.

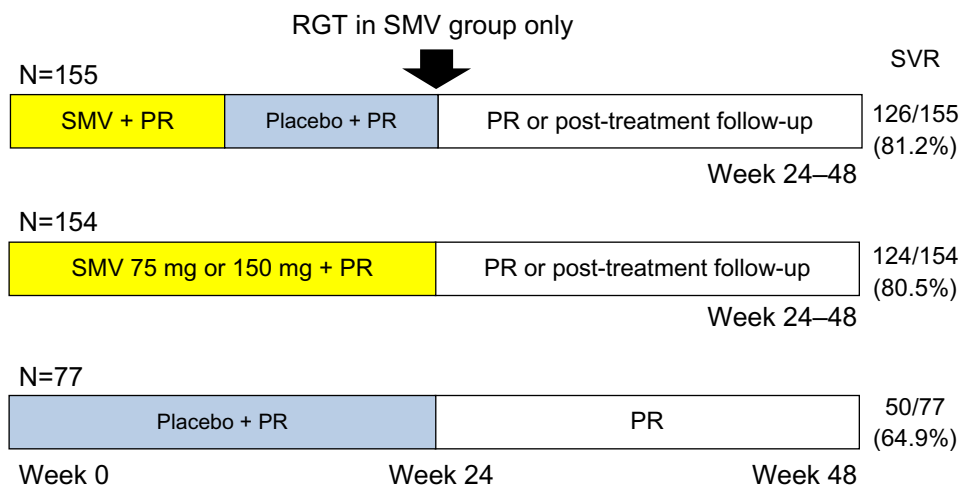


Figure 2 PILLAR study design and results. SVR rates were measured at 24 weeks after the end of treatment.

Notes: RGT algorithm: all therapy of the SMV group was completed at week 24 if hepatitis C virus RNA was <25 IU/mL at week 4 and undetectable at weeks 12, 16, and 20. Data from Fried MW et al.²¹ In the control group, patients received PR (180 µg/week peginterferon; 1,000–1,200 mg/day ribavirin) for 48 weeks.

Abbreviations: PILLAR, Protease Inhibitor TMC435 Trial Assessing the Optimal Dose and Duration as Once-Daily Antiviral Regimen; PR, peginterferon plus ribavirin; RGT, response-guided therapy; SMV, simeprevir; SVR, sustained virologic response.

SVR rates were 83.9% and 50.0%–78.1% with simeprevir 75 mg, 97.1% and 66.7%–80.0% with simeprevir 150 mg, and 100% and 50% in the control group (interleukin 28B [IL28B] major and minor genotype, respectively).²¹ Other than mild reversible hyperbilirubinemia, without serum aminotransferase abnormalities, associated with higher doses of simeprevir, the adverse event profile was similar between simeprevir and control groups.²¹ This study²¹ showed no differences in SVR between the 12- and 24-week durations of simeprevir, and it was also demonstrated that simeprevir allows the majority of treatment-naïve HCV genotype 1 patients to shorten their treatment duration to at least 24 weeks.

Simeprevir with peginterferon plus ribavirin for treatment-naïve HCV genotype 1b patients in Japan

The Phase II, multicenter, double-blind, DRAGON study (A Phase II Study of TMC435 in Patients with Chronic Hepatitis C; NCT00996476) examined the efficacy and safety of two different doses of simeprevir administered QD for two different durations in combination with peginterferon plus ribavirin in treatment-naïve HCV genotype 1b patients.²² A total of 92 patients were randomly assigned to one of five groups (Figure 3): simeprevir (50 mg or 100 mg QD) for 12 or 24 weeks, and peginterferon plus ribavirin. Patients in the simeprevir arms were treated for 24 or 48 weeks according to RGT criteria.

In the simeprevir groups, nine patients permanently discontinued all treatment due to adverse events (8/79, 10%) or

virologic stopping criteria (1/79, 1.3%). In the peginterferon plus ribavirin for 48 weeks group, three patients permanently discontinued all treatment due to adverse events (2/13, 15%) or another reason (1/13, 7.7%).²² Among the simeprevir groups, SVR rates ranged from 83%–90% (Figure 3).²² In the DRAGON study,²² no emerging mutations were observed in the selected NS3 protease domain in the single patient with viral breakthrough. Among ten of eleven simeprevir-treated relapsers, mutations in the NS3 protease domain (Q80R, R155Q, and D168A/C/E/H/V, alone or in combination) emerged in six patients.²² These results showed that simeprevir was highly effective for patients infected with HCV subtype 1b, to which almost all of HCV genotype 1 belongs.²³ The RGT approach might be beneficial for patients in Japan, although the majority of simeprevir-treated patients were eligible to stop all treatment at week 24.²² The addition of simeprevir (100 mg QD) to peginterferon plus ribavirin demonstrated potent antiviral activity and improved the SVR rates with only 24-week treatment duration in treatment-naïve patients infected with HCV genotype 1 in Japan.

Simeprevir with peginterferon plus ribavirin for treatment-experienced HCV genotype 1 patients

The Phase IIb international, randomized, double-blind, placebo-controlled ASPIRE study (Antiviral Stat-C Protease Inhibitor Regimen in Experienced Patients; NCT00980330) evaluated the efficacy, tolerability, and safety of simeprevir QD in combination with peginterferon α-2a plus ribavirin in HCV genotype 1 patients who failed to respond to

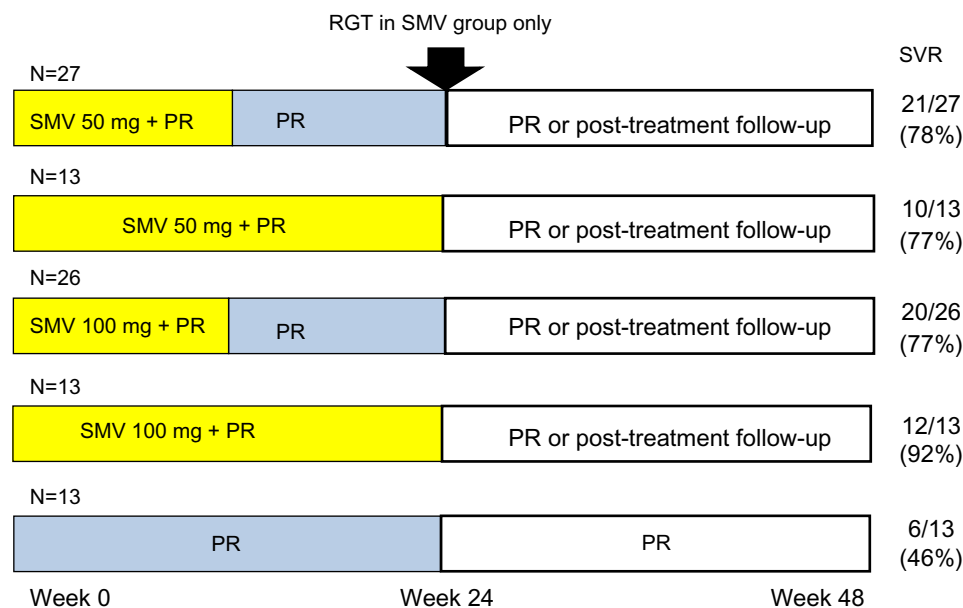


Figure 3 DRAGON study designs and results.

Notes: SVR rates were measured at 24 weeks after the end of treatment. RGT criteria: all therapy of the SMV group was completed at week 24 if hepatitis C virus RNA was $< 1.4 \log_{10}$ IU/mL at week 4 and undetectable at weeks 12, 16, and 20; otherwise PR (180 μ g/week peginterferon α -2a; 600–1,000 mg/day ribavirin) was continued to week 48. In the control group, patients received PR for 48 weeks. Data from Hayashi et al.²²

Abbreviations: DRAGON, A Phase II Study of TMC435 in Patients with Chronic Hepatitis C; PR, peginterferon plus ribavirin; RGT, response-guided therapy; SMV, simeprevir; SVR, sustained virologic response.

previous peginterferon/ribavirin treatment.²⁴ A total of 463 patients who did not respond (null response), had partial response, or relapsed after treatment with peginterferon plus ribavirin were randomly assigned to receive simeprevir (100 or 150 mg QD) for 12, 24, or 48 weeks plus peginterferon and ribavirin for 48 weeks ($n=396$), or placebo plus peginterferon and ribavirin for 48 weeks ($n=66$). SVR rates were significantly higher ($P<0.01$) in the simeprevir groups (61%–80%) than in those given placebo (23%) (simeprevir versus placebo: prior null response, 38%–59% versus 19%; prior partial response, 48%–86% versus 9%; and prior relapse, 77%–89% versus 37%).²⁴

SVR rates were higher in simeprevir-treated patients compared with control irrespective of HCV subgenotype, and were generally higher with simeprevir 150 mg than simeprevir 100 mg. In patients with simeprevir 150 mg, HCV genotype 1a and 1b patients had 63.1% and 80.4% SVR rates, respectively.²⁴ Regarding METAVIR scores, cirrhotic patients (METAVIR score F4) treated with simeprevir 150 mg achieved SVR rates of 73%, 82%, and 31% in prior relapse, prior partial response, and prior null response, respectively, compared with 0% for control patients.²⁴ There might be a benefit with simeprevir in previous null responders who have advanced stages of fibrosis and/or cirrhosis. Regarding *IL28B* genotype rs12979860, the SVR rates with 150 mg were 88% for CC, 74% for CT,

and 61% for TT genotypes (versus 18%, 31%, and 14%, respectively, in the control group).²⁴ Regarding resistance mutations associated with simeprevir treatment, D168V was observed primarily in HCV genotype 1b and R155K in HCV genotype 1a.²⁴ Among patients infected with HCV genotype 1a, the presence of the Q80K polymorphism at baseline did not appear to influence the SVR rate in the simeprevir 150 mg group of the ASPIRE study.²⁴ Mild and transient increases in mean bilirubin were seen during the first weeks of simeprevir treatment. In vitro studies have demonstrated that simeprevir is an inhibitor of the bilirubin transporters OATP1B1 and MRP2.^{22,24} In treatment-experienced patients, 12, 24, or 48 weeks of simeprevir (100 mg QD or 150 mg QD) in combination with 48 weeks of peginterferon plus ribavirin significantly increased SVR rates.

Phase III trials in Japanese patients infected with HCV genotype 1

Four Phase III Japanese studies of simeprevir QD demonstrated SVR 12 weeks after the end of treatment (SVR₁₂) in HCV genotype 1 patients (Figure 4).^{25–27}

In CONCERTO-1 (A Study of the Efficacy of Combination Therapy Including Simeprevir [TMC435] in the Treatment of Genotype 1 Hepatitis C; Figure 4A), 183 treatment-naïve patients were randomized to receive simeprevir or placebo for

12 weeks plus peginterferon α -2a and ribavirin for 24 or 48 weeks. In CONCERTO-2 (A Study of the Efficacy of Retreatment with Simeprevir [TMC435] in the Treatment of Genotype 1 Hepatitis C; Figure 4B), 108 patients who failed to respond to previous treatment were randomized to two groups. In one group, patients received simeprevir plus peginterferon α -2a and ribavirin for 12 weeks, followed by RGT of peginterferon α -2a and ribavirin alone for 12 or 36 weeks. In the other group, patients received simeprevir plus peginterferon α -2a and ribavirin for 24 weeks, followed by RGT of peginterferon α -2a and ribavirin alone for up to 24 weeks. In CONCERTO-3 (A Study of the Efficacy of Retreatment with Simeprevir [TMC435] in the Treatment of Genotype 1 Hepatitis C; Figure 4B), 49 patients with prior relapse received simeprevir and peginterferon α -2a and ribavirin for 12 weeks, followed by RGT of peginterferon α -2a and ribavirin alone for 12 or 36 weeks. In CONCERTO-4 (A Study of the Efficacy of Combination Therapy with Simeprevir [TMC435], Peginterferon α -2b, and Ribavirin in the Treatment of Genotype 1 Hepatitis C; Figure 4C), instead of peginterferon α -2a, peginterferon α -2b was used for a total of 79 patients.²⁷ Simeprevir with peginterferon α -2a/2b plus ribavirin treatment was effective for not only treatment-naïve patients but also prior null responders and relapsers with HCV genotype 1b in Japan.

Phase III trials in treatment-naïve patients infected with HCV genotype 1

The QUEST (Phase III Trial of TMC435 in Treatment-naïve, Genotype 1 Hepatitis C-infected Patients) trials were Phase III, randomized, double-blind studies that evaluated simeprevir with peginterferon α -2a (QUEST-1) or peginterferon α -2a/2b (QUEST-2) plus ribavirin in treatment-naïve HCV genotype 1 adult patients. The pooled analysis consisted of 785 patients (IL28B TT, 14.6%; METAVIR F4, 10.4%; genotype 1a, 48.4%; Q80K+, 16.8%) (QUEST-1, n=394; QUEST-2, n=391).²⁸ The SVR12 rate was significantly superior with simeprevir/peginterferon plus ribavirin versus placebo/peginterferon plus ribavirin (80.4% versus 50.0%; $P<0.001$). In simeprevir-treated patients with rapid virologic response (defined as HCV RNA <25 IU/mL undetectable at week 4), 89.6% achieved SVR12. SVR12 rates of 94.7%, 92.3%, 85.4%, and 83.9% were achieved in patients treated with simeprevir who had IL28B genotype CC, baseline HCV RNA $\leq 800,000$ IU/mL, genotype 1b, and METAVIR F0–F2, respectively.²⁸ High rapid virologic response rates were observed in patients with IL28B minor genotype, METAVIR F4, and Q80K (68.8%, 66.7%, and

63.1%, respectively) with high SVR rates (77.4%, 75.0%, and 79.2%, respectively).²⁸ Results from these studies suggest that simeprevir also conferred clinical benefit among patients with unfavorable baseline characteristics, such as IL28B minor genotype, METAVIR F4, and HCV genotype 1a/Q80K+.

Phase III trials in HCV genotype 1 patients who relapsed after previous interferon-based therapy

The double-blind, multicenter, Phase III PROMISE (Phase III Trial of TMC435 in Genotype 1 Hepatitis C-infected Patients Who Relapsed After Previous Therapy) study evaluated simeprevir plus peginterferon α -2a/ribavirin in HCV genotype 1 patients with prior relapse.²⁹ The “intent-to-treat” population consisted of 393 patients. SVR12 was significantly higher with simeprevir (150 mg QD)/peginterferon α -2a plus ribavirin than placebo/peginterferon α -2a/ribavirin (79.2% versus 36.8%; $P<0.001$). With simeprevir (150 mg QD) treatment, SVR12 was 88.7%, 85.9%, and 82.0% in patients with IL28B CC genotype, HCV genotype 1b, and METAVIR F0–F2, respectively. The incidence and profile of adverse events were generally similar between the simeprevir and placebo treatment groups. Bilirubin increases with simeprevir/peginterferon α -2a plus ribavirin were mild, transient, and without concomitant increases in alanine aminotransferase/aspartate aminotransferase.²⁹ Simeprevir might be useful for the treatment of the different patient subpopulations with prior relapse on interferon, including patients with IL28B minor genotype and METAVIR score F4.²⁹

Other clinical trials with simeprevir

The ATTAIN (An Efficacy, Safety, and Tolerability Study for TMC435 Versus Telaprevir in Combination With Peginterferon α -2a and Ribavirin in Chronic Hepatitis C Patients Who Were Null or Partial Responders to Prior Peginterferon α -2a and Ribavirin Therapy) Phase III trial examined the efficacy, safety and tolerability of simeprevir versus telaprevir in combination with peginterferon α -2a and ribavirin in chronic hepatitis C patients who were null or partial responders to prior treatment.³⁰ The results have not yet been published.

The COSMOS (A Study of TMC435 in Combination With PSI-7977 [GS7977] in Chronic Hepatitis C Genotype 1-Infected Prior Null Responders To Peginterferon/Ribavirin Therapy or HCV Treatment-naïve Patients) Phase II, randomized, open-label study evaluated the efficacy and safety of simeprevir 150 mg QD and sofosbuvir 400 mg QD – an HCV NS5B nucleotide polymerase inhibitor – with or without ribavirin for 12 or 24 weeks in HCV genotype 1 patients with METAVIR

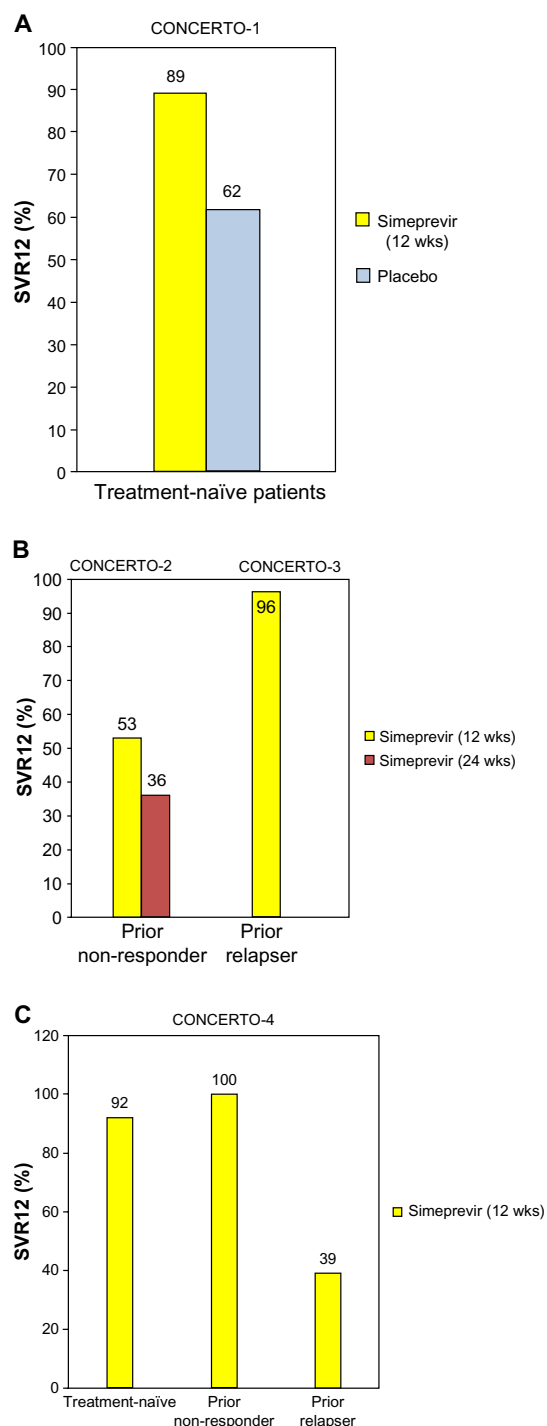


Figure 4 SVR12 in four Phase III Japanese hepatitis C virus genotype 1 patients treated with (A and B) simeprevir and ribavirin plus peginterferon α -2a or (C) peginterferon α -2b. (A) CONCERTO-1 trials for treatment-naïve patients; (B) CONCERTO-2 and CONCERTO-3 trials for prior non-responders and prior relapsers, respectively; and (C) CONCERTO-4 trials for treatment-naïve patients, prior non-responders, and prior relapsers. Data from Hayashi et al,²⁵ Izumi et al,²⁶ and Suzuki et al.²⁷

Abbreviations: CONCERTO-1, A Study of the Efficacy of Combination Therapy Including Simeprevir (TMC435) in the Treatment of Genotype 1 Hepatitis C; CONCERTO-2/3, A Study of the Efficacy of Retreatment with Simeprevir (TMC435) in the Treatment of Genotype 1 Hepatitis C; CONCERTO-4, A Study of the Efficacy of Combination Therapy with Simeprevir (TMC435), Peginterferon α -2b, and Ribavirin in the Treatment of Genotype 1 Hepatitis C; SVR12, sustained virologic response 12 weeks after the end of treatment; wks, weeks.

score F0–F2 who were prior null responders to peginterferon plus ribavirin (cohort 1) or treatment-naïve patients and prior null responders with F3–F4 (cohort 2).³¹ Totals of 80 (cohort 1) and 87 (cohort 2) patients began the treatment. In cohort 1, SVR12 was 96.3% (26/27) and 92.9% (13/14) in patients treated with simeprevir plus sofosbuvir with and without ribavirin for 12 weeks, and SVR12 was 79.2% (19/24) and 100% (14/14) in patients treated with simeprevir plus sofosbuvir with or without ribavirin for 24 weeks.³¹ In cohort 2, SVR4 was 83.3% (20/24) and 93.3% (14/15) in patients treated with simeprevir plus sofosbuvir with and without ribavirin for 12 weeks.³¹ Simeprevir plus sofosbuvir with or without ribavirin for 12 or 24 weeks might result in a high SVR in HCV genotype 1 patients including null responders and patients with cirrhosis.³¹

It was recognized that some “difficult-to-treat” patients would still exist,³² and this would include HCV–human immunodeficiency virus (HIV) co-infected patients. For the shared modes of transmission, 20%–30% of HIV-infected patients in the USA are co-infected with HCV.³³ HIV infection facilitates HCV-related fibrosis progression, increasing the risk of cirrhosis and decompensated liver disease.³⁴ In HCV–HIV patients, the peginterferon plus ribavirin treatment led to only ~20% SVR in HCV genotype 1 patients.^{32–38} Telaprevir- or boceprevir-based triple therapy is a promising option for co-infected patients with well-controlled HIV infection, although these drugs may be associated with severe adverse events.^{39–42} Simeprevir with peginterferon plus ribavirin led to 57% SVR for prior null responders of HCV genotype 1/HIV co-infected patients.⁴³ Overall SVR12 was ~74%. Simeprevir is metabolized by cytochrome P450 3A4 enzyme and preclinical studies showed that it interacts with certain antiretrovirals. In that study, patients were not permitted to use HIV protease inhibitors or efavirenz, and most were on raltegravir and almost all took nucleoside/nucleotide reverse transcriptase inhibitors.⁴³ Simeprevir/peginterferon α -2a plus ribavirin could be useful for the treatment of some “difficult-to-treat” patients.³² Previous studies suggested that amino acid substitutions in the HCV core region are a useful predictor of SVR in the peginterferon plus ribavirin combination treatment in patients infected with HCV genotype 1.^{44–46} Information from both IL28B single nucleotide polymorphism testing and HCV core protein substitutions may yield a more accurate baseline prediction of SVR in simeprevir with peginterferon plus ribavirin therapies.^{47,48} Although simeprevir shows cross-resistance with telaprevir at amino acid positions 155 and 156,^{16,17} most simeprevir-resistant mutations were reported to be at

amino acid position 168.⁴⁹ Further studies will be needed to determine whether simeprevir is effective against the positively selected variants upon antiviral treatment.

Conclusion

This review summarized key preclinical and clinical data of simeprevir – an HCV NS3/4A protease inhibitor, its mechanism of action, resistance mutations, and its efficacy in clinical trials. In the USA, Canada, and Japan, simeprevir and peginterferon plus ribavirin have been approved for the treatment of HCV genotype 1 patients and are now used in daily clinical practice. In general, simeprevir and peginterferon plus ribavirin treatment is highly effective, with adverse events similar to those of peginterferon plus ribavirin, the exception being milder, reversible jaundice. In the near future, interferon-free regimens with simeprevir are sure to shed new light on HCV treatment. New results from clinical trials using simeprevir should be the focus of attention.

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