Simeprevir for the treatment of chronic hepatitis C

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Introduction: The addition of protease inhibitors such as telaprevir and boceprevir with PEGylated interferon and ribavirin has significantly improved cure rates for genotype 1 hepatitis C virus (HCV) infection. Simeprevir (TMC435) is a second-generation protease inhibitor that is in development for the treatment of genotype 1 HCV infection.

Areas covered: The authors present: i) an overview of Phases I – III clinical trials of simeprevir for HCV infection based on peer-reviewed literature and congress presentations and ii) an evaluation of the efficacy and safety of simeprevir in the treatment of HCV infection.

Expert opinion: Simeprevir is a once-daily oral medication that combined with PEGylated interferon and ribavirin appears to be a potent and safe agent to treat genotype 1 HCV infection for patients who are treatment-naïve and prior treatment-failures. Compared to telaprevir and boceprevir, simeprevir will likely be the protease inhibitor of choice for genotype 1 HCV infection based on ease of use, lower rates of adverse events, including rash and anemia, and no significant reported drug-drug interactions. Associated side effects inherent with interferon-based regimens may be problematic for patients. As HCV therapies evolve into interferon-free regimens, simeprevir may potentially be combined with other oral direct-acting agents without interferon to treat HCV infection.

Keywords: chronic hepatitis C, genotype 1, protease inhibitor, simeprevir, TMC435

1. Introduction

Over 150 million persons are infected with chronic hepatitis C (CHC) worldwide, including 5.2 million in the United States [1,2]. The majority of these patients were born between 1945 and 1965, and as that population will now be screened for CHC in the United States, we will likely see many more diagnosed in the next decade. Patients infected with hepatitis C virus (HCV) are at risk of advanced fibrosis and cirrhosis with complications including ascites, hepatic encephalopathy, variceal bleeding and hepatocellular carcinoma. Genotype 1 HCV infection makes up to 70% of patients infected with HCV in the United States.

2. Overview of the market

For the past decade, standard treatment for HCV genotype 1 had been with PEGylated interferon (PEG-IFN) and ribavirin (RBV); however, rates of sustained virological response (SVR) approximated 40 – 50% and significant side effects limited the treatment for a number of patients [3-5].

Major advances have changed the optimal treatment regimen of genotype 1 chronic HCV infection, including the development of direct-acting antiviral (DAA) agents. Four major classes of DAAs are in development as therapy for CHC. These classes include NS3/4A protease inhibitors, NS5B polymerase nucleos(t)ide analogs, NS5B polymerase non-nucleoside analogs and NS5A inhibitors [6]. Presently, only
Box 1. Drug summary

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<thead>
<tr>
<th>Drug name</th>
<th>Simeprevir</th>
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<tr>
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<td>III completed</td>
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<tr>
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<tr>
<td>Pivotal trial(s)</td>
<td>QUEST-1, QUEST-2 and PROMISE [22-24]</td>
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Figure 1. Chemical structure of simeprevir.

Inhibitors of the HCV nonstructural protein 3/4A (NS3/4A) serine protease have been approved by the Food and Drug Administration (FDA) to treat HCV genotype infection, including telaprevir and boceprevir [7].

Telaprevir and boceprevir are potent inhibitors of genotype 1 HCV infection [8-11]. About 750 mg of telaprevir is given orally every 8 h with a fatty meal for 12 weeks along with PEG-IFN and RBV, followed by an additional 12 - 36 weeks of PEG-IFN and RBV. About 800 mg of boceprevir is given with food every 8 h for 24 - 44 weeks preceded by a 4-week lead-in treatment with PEG-IFN and RBV alone. Phase III trials demonstrated overall SVR of 66 - 75% with poorer response seen in African-Americans, cirrhotics and null responders. Adverse events (AEs) that were more frequent in triple therapy compared to PEG-IFN and RBV alone include anemia, rash, dysgeusia, pruritus and nausea. In Phase III trials evaluating telaprevir, a rash of a severity was noted in 56% of patients, and hemoglobin levels of < 10 g/dl were observed in 36% of patients receiving telaprevir-based regimen [8]. A hemoglobin level < 10 g/dl was noted in 49% of patients who received the boceprevir-based regimen [10]. Given these rates of AEs and multiple-daily dosing that need to be accompanied with food, the need to develop other therapies for the treatment of genotype 1 HCV infection remains substantial.

A number of DAAs are being developed to treat genotype 1 HCV infection. Besides simeprevir (Box 1), another DAA that has completed Phase III trials and is currently in review for FDA approval is sofosbuvir, an uridine analog prodrug that acts as a nucleos(t)ide analog. Sofosbuvir is given orally once daily, with or without food, is well tolerated and is highly efficacious. In the NEUTRINO study, a single-group, open-label, Phase III study that combined sofosbuvir with PEG-IFN and RBV for 12 weeks, a SVR12 of 90% was reported [12].

3. Introduction to simeprevir

3.1 Chemistry

The molecular formula for simeprevir is C\textsubscript{38}H\textsubscript{47}N\textsubscript{5}O\textsubscript{7}S\textsubscript{2} and its molecular mass is 749.96 g/mol. Its chemical name using the International Union of Pure and Applied Chemistry (IUPAC) nomenclature is (1R,4R,6S,15R,17R)-N-(cyclopropanesulfonyl)-17-((7-methoxy-8-methyl-2-[4-(propan-2-yl)-1,3-thiazol-2-yl]quinolin-4-yl oxy)-13-methyl-2,14-dioxo-3,13-diazatricyclo[13.3.0.0\textsubscript{4,6}]octadec-7-ene-4-carboxamide. Figure 1 shows the chemical structure of simeprevir.

3.2 Basic and animal pharmacology

Similar to telaprevir and boceprevir, simeprevir is a NS3/4A protease inhibitor. Serine protease NS3/4A is essential to the life cycle of the HCV. The NS3/4A protease mediates the cleavage of four nonstructural HCV proteins, including NS4A, NS4B, NS5A, and NS5B, and inhibiting this enzyme disrupts viral replication. While telaprevir and boceprevir belongs to the class of \(-\)ketoamide electrophilic trap-containing inhibitors, simeprevir belongs to the macrocyclic class of protease inhibitors. In Huh7-Luc cells containing genotype 1b cells, simeprevir potently inhibited HCV replication with half-maximal effective concentration (EC\textsubscript{50}) of 8 nM/l (6 ng/ml) and a selectivity index of 5875 [13]. In rats, simeprevir concentrations were achieved in the liver relative to blood plasma at all time points tested (liver:plasma ratio of 32:1 to 65:1). While plasma exposure dropped to around the EC\textsubscript{50} at 24 h post-dosing, the liver concentration remained above the replicon EC\textsubscript{90} up to 31 h post-dosing, thus suggesting the feasibility of once-daily dosing. The highest tissue/plasma area under the curve (AUC) ratios were observed in the small intestine (ratio of 128), large intestine (ratio of 29) and liver (ratio of 39).

3.3 Pharmacokinetics and metabolism

A Phase I, randomized, double-blind, placebo-controlled trial by Reesink et al. evaluated the safety and pharmacokinetic profile of simeprevir in single and multiple ascending doses in 49 healthy volunteers followed by an open-label, non placebo-controlled panel in six genotype 1 hepatitis C patients [14]. The 49 healthy non-HCV infected subjects were selected and divided into six panels of six to nine subjects each. The six CHC patients with genotype 1 were individuals who had failed previous IFN-based therapy. After the last dose on day 5, the AUC\textsubscript{24 h} for the 200 mg dose group was ~ 10 times higher than that for the 100 mg/day dose group, while the increase in the AUC\textsubscript{24 h} value was 4.7-fold for the dose increase from 200 to 400 mg. A late time to mean peak concentration (T\textsubscript{max}) was observed, with a T\textsubscript{max}...
of 4–6 h and the half-life of 41 h. The mean trough concentrations of TMC435 achieved in the 200 mg/day dosing regimen on day 5 of 1445 ng/ml was >275 times the EC_{50} value as determined by prior in vitro studies (6 ng/ml). In the six genotype 1 HCV infected patients given 200 mg/day of simeprevir for 5 days, the pharmacokinetic profile was similar to healthy volunteers and HCV-RNA levels declined rapidly with >3-log_{10} IU/ml reductions compared with baseline, with a maximal median decrease of HCV-RNA viral load of 3.9 log_{10} IU/ml.

A multicenter, Phase IIa, randomized, blinded, placebo-controlled study by Manns et al. (OPERA-1) evaluated the antiviral activity and pharmacokinetics of simeprevir given for 4 weeks in combination with PEG-IFN and RBV in treatment-naive and treatment-experienced patients with genotype 1 HCV infection [15]. A total of 77 treatment-naive genotype 1 HCV subjects were randomized into two cohorts with each cohort divided into two panels (A and B). Cohort 1 evaluated simeprevir (25 or 75 mg/day) when either given as monotherapy for 1 week followed by 21 days of triple therapy in combination with PEG-IFN and RBV (panel A) or given as triple therapy for 28 days (panel B). In a similar fashion, individuals in cohort 2 were given simeprevir 200 mg/day or placebo for 1 week followed by 21 days of PEG-IFN and RBV (panel A) or 28 days of triple therapy (panel B). In a separate cohort, 39 treatment-experienced genotype 1 HCV subjects were randomized to placebo, simeprevir 75 mg/day, simeprevir 150 mg/day or simeprevir 200 mg/day.

Potent antiviral activity was observed in all cohorts evaluated. In cohorts 1 and 2 involving monotherapy with simeprevir for 7 days, a dose-dependent reduction mean plasma HCV-RNA was observed, with the mean log reduction of 0.02, -2.63, -3.43 and -4.13 log_{10} IU/ml observed for placebo, simeprevir 25, 75 and 200 mg, respectively. The addition of PEG-IFN and RBV increased the antiviral activity during the first 7 days with the mean log reduction of -1.72, -3.47, -4.55 and -6.68 log_{10} IU/ml for placebo, simeprevir 25, 75 and 200 mg, respectively. In a similar fashion, triple therapy resulted in significant decline in HCV viral load, with mean log reduction of -3.64, -4.74, -5.52 and -5.44 at the end of 28 days for placebo, simeprevir 75, 150 and 200 mg, respectively.

Eight patients had viral breakthrough during the first 28 days of treatment. In treatment-naive patients group, breakthrough occurred in five patients who received simeprevir as monotherapy with no cases reported among those who received triple therapy for 28 days. In the cohort with treatment-experienced patients, breakthrough occurred in three non-responders.

Steady-state conditions were reached by day 7 in treatment-naïve and treatment-experienced patients. An increase in plasma concentrations was generally more than dose-proportional, and the difference in the AUC_{24 h} between simeprevir 75 and 200 mg dosing was 9.9-fold. Safety analyses showed a trend for mild increases in direct and indirect bilirubin seen mostly with the 200 mg dose.

Several studies have evaluated the drug-drug interactions which involve simeprevir and drugs that are metabolized by CYP3A4. A Phase I randomized crossover trial examined the pharmacokinetic interactions between simeprevir 150 mg and single doses of cyclosporine 100 mg or tacrolimus 2 mg in 28 healthy volunteers without hepatitis C [16]. The pharmacokinetic profile of simeprevir was similar whether it was given alone or coadministered with cyclosporine or tacrolimus. The C_{max} and AUC for cyclosporine were 16 and 19% higher than when given alone. The changes observed in the pharmacokinetic parameters of cyclosporine and tacrolimus were not clinically relevant as no serious AEs were reported. In a similar fashion, other drugs metabolized by CYP3A4 such as oral contraceptive pills containing ethinyl estradiol and norethindrone did not have any clinically relevant interactions with simeprevir [17].

### 4. Clinical efficacy in HCV infection

In an international, randomized, double-blinded, placebo-controlled Phase Ib trial by Fried et al. (PILLAR), the efficacy and safety of two different doses of simeprevir administered once daily with PEG-IFN/RBV in treatment-naive patients with HCV genotype 1 infection were investigated [18]. Patients were randomized to placebo or simeprevir 75 or 150 mg/day plus PEG-IFN and RBV for 12 or 24 weeks. Patients randomized to 12 weeks of simeprevir therapy received an additional 12 weeks of placebo plus PEG-IFN/RBV. Patients in the simeprevir arms were eligible for a shortened treatment course if response-guided therapy (RGT) criteria were met. This criteria included an HCV-RNA viral load <25 IU/ml (Cobas® Taqman® HCV Test, version 2.0 for Use with High Pure System, Roche Molecular Systems, Pleasanton, CA, USA) at week 4 and undetectable HCV-RNA at weeks 12, 16 and 20. If RGT criteria were met, all therapy was completed at 24 weeks. Patients not meeting RGT continued with PEG-IFN and RBV until week 48, as did all patients in the placebo group. The median age in this trial was 46.5 years, 55% were male, and the patient population was predominantly white. Cirrhotic patients were excluded from this trial. SVR24 rates were 65% in the placebo arm, compared to 71–81% in the simeprevir 75 mg arm and 81–86% in the simeprevir 150 mg arm. The majority of patients (79–86%) treated with simeprevir were able to shorten the total duration of therapy to 24 weeks.

A second international, randomized, double-blinded, placebo-controlled trial by Zeuzem et al. (ASPIRE) compared simeprevir (100 or 150 mg/day) with PEG-IFN/RBV to placebo with PEG-IFN/RBV in 462 treatment-experienced genotype 1 HCV-infected patients [19]. The total duration of placebo arm with PEG-IFN/RBV was 48 weeks. In all the treatment arms (including all simeprevir arms), PEG-IFN
The median body mass index was 27 kg/m². Cirrhotics were a median age of 48 years, 29% had the CC allele genotype 1a/other vs 1b, IL28B allele phenotype (CC vs CT vs TT) and META- VIR fibrosis score (F0 – F2 vs F3 vs F4). Genotypes 1a and 1b HCV subjects on simeprevir attained SVR12 rates of 71 and 90%, respectively, compared to placebo rates of 49 and 52%, respectively. With regard to IL28 genotype those with CC/CT/TT allele on simeprevir achieved SVR12 rates of 94, 76 and 65%, respectively, compared to 78, 42 and 24%, respectively, on placebo. Subjects with METAVIR F0 – F2, F3 and F4 on simeprevir had SVR12 rates of 83, 78 and 58%, respectively, compared to 60, 26 and 29%, respectively, for placebo. Genotype 1a HCV patients with Q80K baseline mutation showed a substantially lower SVR12 rate in the simeprevir group with minimal difference in SVR12 rate between simeprevir plus PEG-IFN/RBV and PEG-IFN/RBV alone (difference of 4.7%; 95% CI: -14.6 to 24.1%), thus suggesting that the mutation inactivated simeprevir in this study. However, of the 63% of such patients who achieved RVR, 74% went on to SVR12.

On-treatment failure and virological relapse were decreased with simeprevir arm compared to placebo arm (9 vs 34% and 9 vs 21%, respectively). In these patients, mutations were detected in the NS3 protease domain in the simeprevir arm, including R155K alone or in combination with mutations at positions 80 and/or 168 for genotype 1a and D168V in genotype 1b.

A randomized, double-blinded, placebo-controlled Phase III trial by Manns et al. (QUEST-2) also evaluated the efficacy and safety of simeprevir plus PEG-IFN/RBV in treatment-naive patients with genotype 1 HCV infection [23]. Subjects were randomized to either simeprevir 150 mg/day or placebo for 12 weeks in combination with PEG-IFN-α-2a or -α-2b for total duration of treatment of 24 or 48 weeks depending on response-guided criteria. Similar to QUEST-1, the total duration of therapy in the simeprevir arm was 24 weeks, if the HCV-RNA load was < 25 IU/ml at week 4 and undetectable viral load at week 12 (Cobas® Taqman® HCV Test, version 2.0 for Use with High Pure System, Roche Molecular Systems, Pleasanton, CA, USA). Simeprevir/placebo was discontinued if HCV-RNA was > 1000 IU/ml at week 4, while PEG-IFN/RBV was continued. All treatment was discontinued if a < 2 log_{10} IU/ml reduction in HCV-RNA from baseline was observed at week 12 or if HCV-RNA was confirmed ≥ 25 IU/ml at week 24 or week 36. The majority of patients were white (87% in simeprevir arm and 94% in placebo arm), with a median age of 48 years, 29% had the IL-28B CC allele genotype, 56% were male and 56% had genotype 1a infection. The median body mass index was 27 kg/m². Cirrhotics were enrolled in this trial (12% in the simeprevir arm and 13% in the placebo arm).

SVR12 was achieved in 80% in the simeprevir arm (210/264) compared with 50% in the placebo arm (65/130, p < 0.001). About 80% (202/254) of patients who were treated with simeprevir achieved rapid virological response (RVR), defined as undetectable HCV viral load after 4 weeks of therapy and of these patients, 91% (181/202) attained SVR12. About 85% of patients who received simeprevir qualified for the shorter 24-week course of therapy. Among the simeprevir recipients who did not meet RGT criteria, only 21% achieved SVR12 within 48 weeks of therapy. The simeprevir arm was superior to control regardless of baseline viral level (HCV-RNA levels ≤ 800,000 IU/ml vs > 800,000 IU/ml), gender, HCV genotype (1a/other vs 1b), IL28B allele phenotype (CC vs CT vs TT) and META-VIR fibrosis score (F0 – F2 vs F3 vs F4). Genotypes 1a and 1b HCV subjects on simeprevir attained SVR12 rates of 71 and 90%, respectively, compared to placebo rates of 49 and 52%, respectively.
The majority of patients (91.4%) in the simeprevir arm qualified for the shorter 24-week therapy course and SVR12 among these patients was 86%. Among the 8.6% of simeprevir-treated patients who did not meet response-guided criteria, 31.8% went on to attain SVR12 within 48 weeks of treatment. About 65% of cirrhotics attained SVR12 with simeprevir compared to 40% with placebo. As noted in QUEST-1, the simeprevir arm was superior to placebo with regard to gender, viral load, HCV genotype, IL-28B genotype and fibrosis. Specifically, genotypes 1a and 1b HCV patients on simeprevir achieved SVR12 rates of 80.4 and 82%, respectively, compared to placebo rates of 45.6 and 53.2%, respectively (p < 0.001). Those with CC/CT/TT allele on simeprevir achieved SVR12 rates of 96, 80.3 and 57.5%, respectively, compared to 81% (p = 0.003), 40% (p < 0.001) and 19% (p < 0.001), respectively, on placebo. Subjects with METAVIR F0–F2, F3 and F4 on simeprevir had SVR12 rates of 84.6, 66.7 and 64.7%, respectively, compared to 51% (p < 0.001), 52.9% (p < 0.001) and 40% (p < 0.001), respectively, for placebo. In contrast to QUEST-1, logistic regression model confirmed higher SVR12 rate with simeprevir compared to placebo in patients who had Q80K mutation at baseline. About 88% of those who received PEG-IFN-α-2a achieved SVR12, while 78% of those who received PEG-IFN-α-2b achieved SVR12. Rates of on-treatment failure and relapse were lower with the simeprevir arm compared to placebo arm (7 vs 32% and 13 vs 24%, respectively).

A third international, multicenter, double-blinded, placebo-controlled Phase III trial by Lawitz et al. (PROMISE) evaluated simeprevir given to treatment-experienced genotype 1 HCV-infected individuals who had previously relapsed after a prior course of IFN-based therapy for at least 24 weeks [24]. Patients were randomized to receive simeprevir or placebo for 12 weeks plus PEG-IFN and RBV for 24 or 48 weeks, depending on response. The same RGT criteria for QUEST-1 and QUEST-2 were applied in PROMISE. All individuals in the placebo arm received 48 weeks of PEG-IFN/RBV. The majority of subjects were males (65%), most were white and the median age was 52 years. Roughly, 75% of subjects had unfavorable IL28B genotype alleles (CT or TT allele).

Overall, 79% in the simeprevir arm achieved SVR12 compared with 37% in the placebo arm. About 93% of patients were qualified to stop treatment at week 24. Those who were genotype 1a attained SVR12 rates of 70%, while those with genotype 1b attained SVR12 rates approaching 86%. Those with IL28B genotype CC allele achieved SVR12 rates of 89%, compared to 79% with the CT allele and 65% with the TT allele. These SVR rates were better than those who received PEG-IFN and RBV: 53% for CC allele (p < 0.001), 34% with CT allele (p < 0.001) and 19% with TT allele (p < 0.001). Among patients with METAVIR scores of F3 and F4, 73 and 74% of patients treated with simeprevir achieved SVR12, in contrast with the patients receiving placebo: 20% for METAVIR F3 (p < 0.001) and 26% for METAVIR F4 (p < 0.001). Roughly, 3% of the simeprevir arm experienced on-treatment failure, compared to 19% receiving placebo. In addition, 19% in the simeprevir arm experienced post-treatment relapse, in contrast to 48% of those who received placebo with PEG-IFN and RBV.

Table 1 summarizes the results from the three pivotal Phase III trials evaluating simeprevir in genotype 1 HCV individuals.

Studies evaluating IFN-free regimens with simeprevir are ongoing. In a Phase IIa study combining simeprevir with sofosbuvir, a NS5B nucleotide analog polymerase inhibitor, with or without RBV (COSMOS) [25], subjects received simeprevir 150 mg/day with sofosbuvir 400 mg/day with or without RBV for either 12 or 24 weeks. This trial consisted of two cohorts: cohort 1 which included prior null responders with METAVIR scores F0–F2, and cohort 2 which included treatment-naive and prior null responders with METAVIR scores F3–F4.

The majority of participants in this trial were men, 71% were white and the median age was 56 years. Almost all patients had unfavorable IL28B polymorphisms associated with poor response to standard PEG-IFN and RBV treatment, including 70% who were CT allele and 24% who were TT allele. About 78% of patients had genotype 1a HCV infection, while the other 22% of patients were genotype 1b. Roughly, 85% of participants who received simeprevir, sofosbuvir and RBV for 12 weeks achieved RVR, similar to those receiving this regimen for 24 weeks (82%). Corresponding RVR rates for dual therapy with only simeprevir and sofosbuvir without RBV for 12 and 24 weeks were 57 and 67%, respectively. All participants (100%) in both 12-week arms of simeprevir and sofosbuvir with and without RBV attained undetectable HCV-RNA at the end of treatment, with similar rates in the 24-week arms (83% with RBV-containing regimen and 90% in the RBV-free regimen). All 24 participants who reached the 12-week post-treatment point attained SVR12. SVR4 rates were 96 and 93% in the 12-week RBV-containing and RBV-free treatment arms, respectively.

5. Safety and tolerability

Simeprevir appears to be well tolerated. In OPERA-1, the most common AEs were fatigue, nausea, asthenia, diarrhea and dry skin in treatment-naive patients. In patients who were treatment-experienced, the most common AEs were dyspnea and influenza-like illness. Two treatment-experienced patients receiving 200 mg/day reported grade 3 AEs: one of whom experienced both indirect and direct hyperbilirubinemia and the other experienced fatigue and influenza-like illness. No grade 4 AE was reported, and only one patient in cohort 5 had to discontinue treatment due to an AE. In the other cohorts, there were no TMC435 treatment discontinuations but there were patients who had to stop PEG-IFN/RBV treatment due to AEs.

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**Table 1**

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<tr>
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<th>PROMISE</th>
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<tr>
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**Simeprevir**

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In QUEST-1, only 3% of patients had to discontinue simeprevir, which was identical to the placebo arm. Roughly, 72% had grade 1 or grade 2 AEs with simeprevir compared to 65% with placebo. AEs included fatigue (40 vs 38% for placebo), headache (31 vs 37% for placebo) and pruritus (21 vs 11% for placebo). Other AEs included rash (27 vs 25% for placebo), anemia (16 vs 11% for placebo), neutropenia (19 vs 11% for placebo), bilirubin increase (9 vs 4% for placebo) and photosensitivity (3 vs 1% for placebo). The bilirubin increase seen in the simeprevir arm was mild and transient and was not associated with an increase in other liver parameters such as aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase.

In QUEST-2, there was no substantial difference in the incidence of AEs between the simeprevir and placebo arms. The most common AEs seen were headache (37 vs 33% for placebo), fatigue (34 vs 38% for placebo), pyrexia (30 vs 35% for placebo) and flu-like symptoms (25 vs 25% for placebo). Other notable AEs included rash (23 vs 11% for placebo), pruritus (17 vs 14% for placebo), anemia (13 vs 15% for placebo) and photosensitivity (3 vs 0.7% for placebo). The rash was mild or moderate in the majority of cases (97%), which was defined as localized skin eruption (grade 1) or diffuse skin eruption involving up to 50% of the body surface area (grade 2). A very severe rash such as Steven’s-Johnson syndrome has not been reported. Similar to QUEST-1, the bilirubin increase seen in subjects treated with simeprevir in QUEST-2 was mild and transient and not associated with an increase in other liver parameters. Discontinuation rates were low with 1.6% in the simeprevir arm having to discontinue simeprevir due to AEs compared to 0.7% in the placebo arm.

In PROMISE, the most common AEs seen were fatigue, headache and influenza-like symptoms which were similar in both simeprevir and placebo arms. Adverse effects which were slightly more common in simeprevir compared to placebo include rash (19 vs 14% for placebo), itching (24 vs 17% for placebo), anemia (11 vs 6% for placebo), bilirubin increase (6 vs 2% for placebo) and photosensitivity (4 vs 0% for placebo).

6. Regulatory affairs

A New Drug Application for simeprevir was submitted on 28 March 2013, and in May 2013, the US FDA granted an expedited review to simeprevir for the treatment of genotype 1 CHC infection.

7. Conclusion

Simeprevir is a protease inhibitor with high efficacy in treating genotypes 1a and 1b HCV infection in treatment-naive and treatment-experienced patients. Given orally, simeprevir 150 mg/day is safe and generally well tolerated. Phase III trials have demonstrated that simeprevir is much superior compared to PEG-IFN and RBV alone – the standard of care for genotype 1 HCV infection – when these trials were first initiated.

8. Expert opinion

Simeprevir is one among a number of medications in the pipeline that will be available for use for chronic HCV infection. Its mechanism of action is similar to other protease inhibitors such as telaprevir and boceprevir which are currently FDA-approved to treat genotype 1 HCV infection. Based on several Phase III trials, simeprevir is highly effective in treating treatment-naive and treatment-experienced patients. In addition to being highly efficacious, simeprevir also appears to be safe with relatively low AEs. For these reasons, simeprevir will likely be approved by FDA to treat genotype 1 HCV infection at the end of 2013 or early 2014. The incidence of anemia and rash appears to be lower compared to telaprevir and boceprevir. Unlike telaprevir and boceprevir, which need to be administered every 8 h with a fatty meal or snack, simeprevir can be taken as once-daily dosing with food. This should theoretically improve patient compliance.
compliance with HCV therapy. Finally, there does not seem to be any significant drug-drug interaction that has been reported with simeprevir. Unlike boceprevir and telaprevir, which inhibits CYP3A4 and P-glycoprotein both in the gut and liver, simeprevir is a weak inhibitor of CYP3A4 and P-glycoprotein only in the gut and not in the liver.

For the abovementioned reasons, including ease of use, lower rates of AEs and less drug-drug interactions, simeprevir will clearly be a superior therapy than boceprevir and telaprevir for genotype 1 HCV infection. Based on the results from Phase III trials, knowledge about the IL28B genotype and level of fibrosis may be helpful for counseling purposes and in deciding whether or not to initiate treatment with simeprevir. The decision to use simeprevir for those patients with METAVIR F2 disease will need to be made on an individual basis.

However, several questions still remain unanswered. While the PROMISE trial looked at relapsers to prior therapy with IFN, there are no reported Phase III trials evaluating the effectiveness of simeprevir in patients who have failed previous treatments, such as those with viral breakthrough, partial responders and null responders. In addition, simeprevir has not yet been studied in some difficult-to-treat groups such as HIV co-infection, post-liver transplant and renal failure. Finally, in QUEST-1, there was no clear benefit for genotype 1a HCV-infected patients with a baseline Q80K mutation treated with simeprevir/PEG-IFN/RBV compared to PEG-IFN/RBV regimen alone. This may be clinically relevant. At this time, it is unclear if the FDA will recommend pretreatment viral sequencing to select patients without this mutation, as there are no FDA-approved sequencing assays currently available.

Sofosbuvir is another HCV medication that along with simeprevir is now pending FDA approval. Based on the NEUTRINO study, sofosbuvir will also likely be approved for treatment-naïve genotype 1 HCV infection at the end of 2013 or early 2014. Both simeprevir and sofosbuvir will likely be approved for use only in combination with PEG-IFN and RBV for 12 weeks for genotype 1 HCV infection. In addition, both medications have extremely high SVR rates. However, the total duration of therapy differs between the two medications: the sofosbuvir-based regimen is completed after 12 weeks of sofosbuvir/PEG-IFN/RBV; in contrast, PEG-IFN/RBV will need to be given for an additional 12 or 36 weeks for those treated with simeprevir according to the RGT algorithm. Another distinction is that sofosbuvir has not been studied in treatment-experienced relapers while this group has been studied with simeprevir. Finally, the costs of both drugs are not available. All of these factors will need to be weighed by the clinician when deciding between simeprevir and sofosbuvir to treat genotype 1 HCV infection. Combining simeprevir, sofosbuvir and RBV as an IFN-free regimen has shown impressive results; however, this regimen is not approved by FDA and thus will not likely be covered completely by payors routinely.

Current HCV therapies that use PEG-IFN will likely be replaced by IFN-free regimens in the next few years in the United States. This will benefit individuals who do not want to experience the side effects associated with IFN as well as those who have been treated with IFN in the past and are IFN-intolerant. Studies combining simeprevir with other oral direct-acting agents without IFN to treat HCV infection are underway, including combining simeprevir and daclatasvir, a NS5A inhibitor with or without RBV [26] as well as simeprevir and IDX719, another NS5A inhibitor with RBV [27].

**Declaration of interest**

PJ Pockros has acted as a speaker for Gilead, Vertex, Merck and Genetech; an advisor for Gilead, Vertex, Merck, Genetech, Janssen, Bristol-Myers Squibb, Abbott and Boehringer Ingelheim, and has received research grants from Gilead, Vertex, Genetech, Janssen, Bristol-Myers Squibb, Abbott, Boehringer Ingelheim and Novartis. DM You has no conflict of interest.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.
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