Simeprevir Increases Rate of Sustained Virologic Response Among Treatment-Experienced Patients With HCV Genotype-1 Infection: A Phase IIb Trial

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BACKGROUND & AIMS: Simeprevir (TMC435) is an oral NS3/4 protease inhibitor in phase III trials for chronic hepatitis C virus (HCV) infection. We performed a phase IIb, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the combination of simeprevir, peginterferon-α2a (PegIFN), and ribavirin (RBV) in patients with HCV genotype-1 infection previously treated with PegIFN and RBV. **METHODS:** We analyzed data from patients who did not respond (null response), had a partial response, or relapsed after treatment with PegIFN and RBV, randomly assigned to receive simeprevir (100 or 150 mg, once daily) for 12, 24, or 48 weeks plus PegIFN and RBV for 48 weeks (n = 396), or placebo plus PegIFN and RBV for 48 weeks (n = 66). All patients were followed for 24 weeks after planned end of treatment; the primary end point was the proportion of patients with sustained virologic response (SVR; undetectable HCV RNA) at that time point. **RESULTS:** Overall, rates of SVR at 24 weeks were significantly higher in the groups given simeprevir than those given placebo (61%–80% vs 23%; $P < .001$), regardless of prior response to PegIFN and RBV (simeprevir vs placebo: prior null response, 38%–59% vs 19%; prior partial response, 48%–86% vs 9%; prior relapse, 77%–89% vs 37%). All groups had comparable numbers of adverse events; these led to discontinuation of simeprevir or placebo and/or PegIFN and RBV in 8.8% of patients given simeprevir and 4.5% of those given placebo. **CONCLUSIONS:** In treatment-experienced patients, 12, 24, or 48 weeks simeprevir (100 mg or 150 mg once daily) in combination with 48 weeks PegIFN and RBV significantly increased rates of SVR at 24 weeks compared with patients given placebo, PegIFN, and RBV and was generally well tolerated. ClinicalTrials.gov number: NCT00980330.

Keywords: Direct-Acting Antivirals; DAA; Clinical Trial; SVR24.

Up to 170 million people globally are currently infected with hepatitis C virus (HCV).[1] In the United States and Europe, it is now associated with a mortality rate surpassing that of human immunodeficiency virus infection.[2–4] During the past decade, the standard of care treatment for chronic HCV infection has been a combination of peginterferon-α (PegIFN-α) and ribavirin (RBV) for 24–48 weeks.[2,5] The limitations of this therapeutic approach are well known, however, and include suboptimal response rates (approximately 40%–50%) in patients infected with HCV genotype 1,[5–7] the most common genotype in the United States and Europe.[8] In addition, response rates in genotype-1–infected patients treated with PegIFN-α/RBV for a second time after initially failing to respond were 7%–22%.[9,10]

A new era in HCV treatment has emerged with the approval of direct-acting antivirals that specifically inhibit the HCV NS3/4A viral protease. Triple therapy consisting of a protease inhibitor combined with PegIFN-α/RBV substantially improves sustained virologic response (SVR) rates compared with PegIFN-α/RBV alone in both treatment-naïve and treatment-experienced patients. SVR rates of approximately 30%–40% with a prior null response to PegIFN-α/RBV, approximately 40%–60% with a prior partial response, and approximately 70%–85% with prior relapse have been observed in patients.[11–13] Improvements in efficacy have come with new treatment challenges, including increased rates of adverse events (AEs), such as anemia and rash, and a complex, multiple-times-daily dosing schedule.[8,11,13,14]

Abbreviations used in this paper: **AE, adverse event; EOT, end of treatment; FSS, Fatigue Severity Scale; HCV, hepatitis C virus; PegIFN, peginterferon-α2a; PegIFN-α, peginterferon-α; RBV, ribavirin; RVR, rapid virologic response; SVR, sustained virologic response; SVR24, sustained virologic response at 24 weeks after the planned end of treatment.**

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Simeprevir (TMC435) is an investigational, single-pill, once-daily, oral HCV NS3/4A protease inhibitor currently in clinical development for the treatment of HCV infection. In phase I and II trials in HCV genotype-1–infected, treatment-naïve and treatment-experienced patients, simeprevir combined with PegIFN-α/RBV was generally well tolerated, with potent antiviral activity, and a pharmacokinetic profile that supports once-daily dosing.[15–19]

The ASPIRE (Antiviral STAT-C Protease Inhibitor Regimen in Experienced Patients) study (TMC435-C206; NCT00980330) was an international, phase IIb, randomized, double-blind, placebo-controlled trial evaluating the efficacy, tolerability, and safety of simeprevir once-daily in combination with peginterferon-α2a (PegIFN)/RBV in patients infected with HCV genotype 1 who have failed to respond to previous PegIFN-α/RBV treatment.

Materials and Methods

Patient Population

Adult patients, aged 18 to 70 years, chronically infected with HCV genotype 1 and with plasma HCV RNA >10,000 IU/mL at screening were included in the study. All patients must have received at least one prior course of PegIFN-α/RBV for $\geq$12 consecutive weeks and not discontinued therapy due to tolerability. Key exclusion criteria included decompensated liver disease, any other liver disease of non-HCV etiology, and infection/co-infection with nongenotype 1 HCV (see Supplementary Material). The METAVIR algorithm was used in this study, with F3 and F4 indicating bridging fibrosis and cirrhosis, respectively.

Study Design

ASPIRE was an international, phase IIb, randomized, 7-arm, double-blind, placebo-controlled trial comparing the efficacy, tolerability, and safety of simeprevir plus PegIFN/RBV with PegIFN/RBV alone in patients with genotype-1 HCV infection who had failed to respond to at least one prior course of PegIFN-α/RBV. Eligible patients from 14 countries in Europe, North America, Australia, and New Zealand were randomized in an equal ratio to 1 of 7 treatment groups (Supplementary Figure 1). Patients were stratified by genotype-1 subtype (1a, 1b, or other) and prior PegIFN/RBV treatment response, classified as having either a prior null response (<2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12 compared with baseline), a prior partial response ($\geq$2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12 compared with baseline, but detectable HCV RNA at the end of treatment [EOT]), or a prior relapse (HCV RNA undetectable at EOT, but detectable within 24 weeks post-treatment).

All patients were to be treated for 48 weeks and followed until week 72 (Supplementary Figure 1). Treatment groups 1 and 2 received 12 weeks of simeprevir (100 mg and 150 mg, respectively) plus PegIFN/RBV, followed by 36 weeks of PegIFN/RBV; treatment groups 3 and 4 received 24 weeks of simeprevir (100 mg and 150 mg, respectively) plus PegIFN/RBV, followed by 24 weeks of PegIFN/RBV; treatment groups 5 and 6 received 48 weeks of simeprevir (100 mg and 150 mg, respectively) plus PegIFN/RBV. In all simeprevir treatment arms, when patients were not receiving simeprevir, they received a matched placebo. Patients in treatment group 7 (placebo control group; referred to as "placebo" or "placebo group" throughout) received 48 weeks of simeprevir-matched placebo plus PegIFN/RBV. For all patients, the 48-week treatment period was followed by post-treatment follow-up for up to 72 weeks after treatment initiation.

PegIFN was administered as a subcutaneous injection (180 μg once weekly), RBV as oral tablets (1000 or 1200 mg/d, depending on body weight), and simeprevir as one oral tablet once daily. Dose adjustments for PegIFN and RBV were permitted in accordance with the manufacturer's prescribing information (see Supplementary Material).

In accordance with the protocol-defined virologic stopping rules, patients with an insufficient response to treatment, ie, not achieving $\geq$1 $\log_{10}$ reduction from baseline in HCV RNA at week 4, $\geq$2 $\log_{10}$ reduction from baseline in HCV RNA at week 12, or HCV RNA $\geq$25 IU/mL detectable at weeks 24 or 36, discontinued all study medication (simeprevir/placebo and PegIFN/RBV). Study medication was also discontinued in the case of viral breakthrough (confirmed, on-treatment increase in HCV RNA of >1 $\log_{10}$ IU/mL from the lowest level reached, or confirmed HCV RNA of >100 IU/mL in patients with HCV RNA previously below the lower limit of quantification of 25 IU/mL or undetectable) at any time point during treatment.

The study took place between September 2009 and August 2011 and was conducted in accordance with the 2008 Declaration of Helsinki, consistent with Good Clinical Practice guidelines and applicable regulatory requirements. All patients provided written informed consent to participate, and the study protocol was reviewed by an Independent Ethics Committee/Institutional Review Board.

Efficacy Assessments

HCV RNA was measured using real-time polymerase chain reaction, with the Roche COBAS TaqMan HCV/HPS assay system version 2.0 (Roche, Basel, Switzerland; lower limit of quantification 25 IU/mL and limit of detection 15 IU/mL for genotype 1). Additional details are provided in the Supplementary Material.

Virologic Assessments

HCV genotype/subtype was determined at baseline using an NS5B sequence-based assay.[20] The impact of the naturally occurring NS3 Q80K polymorphism, which confers low-level resistance to simeprevir (7.7-fold change in median inhibitory concentration as a single amino acid substitution in a genotype-1b replicon) on SVR as well as the emergence of viral variants carrying NS3 amino acid substitutions in patients not achieving SVR were investigated[21] (see Supplementary Material).

Exploratory Host DNA Genotyping

DNA genotyping was performed to explore associations between host genetic polymorphisms and virologic response. For patients who provided written informed consent, a blood sample was collected at baseline and analyzed for genetic polymorphisms, including *IL28B* gene polymorphisms (locus rs12979860).