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CLINICAL—LIVER

Simeprevir With Peginterferon and Ribavirin Leads to High Rates of SVR in Patients With HCV Genotype 1 Who Relapsed After Previous Therapy: A Phase 3 Trial

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See related article, Rodriguez-Torres M et al, on page 1029 in *CGH*.

BACKGROUND & AIMS: Simeprevir is an oral, once-daily inhibitor of hepatitis c virus (HCV) protease NS3/4A. We investigated the safety and efficacy of simeprevir with peg-interferon α-2a and ribavirin (PR) in a randomized, double-blind, placebo-controlled, phase 3 trial of patients with HCV genotype 1 infection who relapsed after previous interferon-based therapy. **METHODS:** Patients were assigned randomly (2:1) to groups given simeprevir (150 mg, once daily) and PR (n = 260) or placebo and PR (n = 133) for 12 weeks. Patients then were given PR alone for 12 or 36 weeks (simeprevir group, based on response-guided therapy criteria) or 36 weeks (placebo group). **RESULTS:** Simeprevir and PR was significantly superior to placebo and PR; rates of sustained virologic response 12 weeks after planned end of treatment (SVR12) were 79.2% vs 36.1%, respectively (43.8% difference; 95% confidence interval, 34.6–53.0; $P < .001$). Among patients given simeprevir, 92.7% met the response-guided therapy criteria and were eligible to complete PR at week 24; of these, 83.0% achieved SVR12. HCV RNA was undetectable at week 4 in 77.2% of patients given simeprevir and 3.1% given placebo. On-treatment failure and relapse rates were lower among patients given simeprevir and PR than those given placebo and PR (3.1% vs 27.1%, and 18.5% vs 48.4%, respectively). Patients given simeprevir did not have adverse events beyond those that occurred in patients given PR alone. Most adverse events were grades 1/2; the prevalence of anemia and rash was similar in both groups. Patients in both groups reported similar severity of fatigue and functional impairments during the study, but duration was reduced among patients given simeprevir. **CONCLUSIONS:** In a phase 3 trial of patients who had relapsed after interferon-based therapy, the addition of simeprevir to PR was generally well tolerated, with an SVR12 rate of 79.2%. Most patients (92.7%) receiving simeprevir were able to shorten therapy to 24 weeks. ClinicalTrials.gov number: NCT01281839.

Keywords: PROMISE; Chronic Hepatitis C; Drug; DAA.

Approximately 150 million individuals worldwide are chronically infected with hepatitis C virus (HCV), with 350,000 people dying annually of HCV-related conditions.[1] Historically, the standard of care for chronic HCV infection was peginterferon (PegIFN)α and ribavirin (RBV).[2–4] However, 50%–60% of HCV genotype 1–infected patients do not achieve sustained virologic response (SVR) with PegIFNα/RBV,[5,6] and up to 32% of responders relapse after cessation of therapy.[7] Re-treatment of relapsed patients with PegIFNα/RBV has SVR rates of approximately 20%–50%.[8–10]

The direct-acting antiviral agents (DAAs), boceprevir and telaprevir, can improve SVR rates when dosed with PegIFNα/RBV,[11–14] with the potential for a shorter treatment duration in some patients.[11,13,15] The telaprevir 50% inhibitory concentration (IC_{50}) values in a genotype 1b HCV replicon and in genotype 1a HCV-infected human fetal hepatocytes were 354 nmol/L and 280 nmol/L, respectively,[16] whereas the boceprevir median effective concentration (EC_{50}) in a genotype 1b HCV replicon was approximately 200 nmol/L, with an approximately 2-fold lower value in a genotype 1a HCV replicon.[17] Data concerning the efficacy of response-guided treatment (RGT) with telaprevir in patients who have relapsed after prior IFN-based therapy are

Abbreviations used in this paper: **AE, adverse event; CI, confidence interval; DAA, direct-acting antiviral agent; EC_{50}, median effective concentration; EOT, end of treatment; FDA, Food and Drug Administration; HCV, hepatitis C virus; IQR, interquartile range; PegIFN, peginterferon; PR, peginterferon α-2a/ribavirin; RBV, ribavirin; RGT, response-guided treatment; RVR, rapid virologic response; SAE, serious adverse event; SVR, sustained virologic response; SVR12, sustained virologic response at 12 weeks; SVR24, sustained virologic response at 24 weeks.**

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lacking. Boceprevir must be administered as 4 pills, 3 times daily, whereas telaprevir must be administered 2 or 3 times daily (6 pills in total).[18] Boceprevir and telaprevir also are associated with a high incidence of adverse events (AEs), including anemia, rash, and renal dysfunction.[19–22] Recently, the nucleotide analog NS5B polymerase inhibitor sofosbuvir also was approved for the treatment of chronic HCV infection in the United States and Europe, representing an improvement on first-generation DAAs.[23,24]

Simeprevir (TMC435) is administered orally, once daily, as a single pill[25]; has been approved in Japan, Canada, the United States and Russia; and is under regulatory review in Europe for the treatment of chronic HCV infection. The median simeprevir EC_{50} and EC_{90} values against a HCV genotype 1b replicon were 9.4 and 19 nmol/L, respectively.[26] Activity of simeprevir against a selection of genotype 1a (N = 78) and 1b (N = 59) chimeric replicons carrying NS3 sequences from HCV NS3/4A protease inhibitor-naive subjects resulted in median fold change in EC_{50} of 1.4 (interquartile range [IQR], 0.8–11) and 0.4 (IQR, 0.3–0.7), compared with reference genotype 1b replicon. Genotype 1a (N = 33) and 1b (N = 2) isolates with a baseline Q80K polymorphism, a naturally occurring NS3 polymorphism that confers low-level resistance to simeprevir, resulted in a median fold change in simeprevir EC_{50} of 11 (IQR, 7.4–13) and 8.4, respectively.

Simeprevir has antiviral activity in patients infected with HCV genotypes 1, 2, 4, 5, and 6,[27–30] and is being evaluated in both PegIFNα/RBV and IFN-free combinations.[27,28,31–34] Simeprevir in combination with PegIFNα/RBV showed SVR rates of approximately 80% in phase 3 trials in treatment-naive patients with HCV genotype 1 infection, with most patients (>84%) able to reduce their treatment duration to 24 weeks.[33,34] In these studies, no additional AEs were observed with simeprevir compared with those seen with PegIFNα/RBV alone.

Results of the PROtease inhibitor TMC435 In patientS who have previously rElapsed on IFN/RBV (PROMISE) study, a randomized, double-blind, placebo-controlled, phase 3 trial undertaken to assess the efficacy, safety, and tolerability of simeprevir with PegIFNα-2a/RBV (PR) for the treatment of chronic HCV genotype 1 infection in patients who had relapsed after previous IFN-based therapy, are presented.

Materials and Methods

Patients

Patients were enrolled at study sites in 14 countries across North America, Europe, and the Asia–Pacific region. Eligible patients were adults (≥18 y) with confirmed genotype 1 HCV infection and screening plasma HCV-RNA levels greater than 10,000 IU/mL, who had relapsed after 24 weeks or more of IFN-based therapy (undetectable HCV-RNA at end of treatment [EOT] or within 2 months after EOT, with documented relapse within 1 year after therapy). A liver biopsy specimen obtained within 3 years of screening showing histology consistent with chronic HCV infection was required, according to the 2010 Food and Drug Administration (FDA) Guidance for Industry on developing DAAs (available from the FDA). Biopsy specimens indicating a METAVIR score of F0–F3 within 3 years of screening, or a score of F4 at any previous time, were acceptable. In total, 68% of patients had a biopsy within a year of screening. Subjects with bridging fibrosis (F3) or cirrhosis (F4) were eligible if they had an ultrasound performed within 6 months before screening (or between the screening and baseline visit) with no findings suspicious for hepatocellular carcinoma. Patients with hepatic decompensation; non–HCV-related liver disease; co-infection with human immunodeficiency virus, hepatitis B virus, or non–genotype 1 HCV; defined laboratory abnormalities (Supplementary Materials and Methods section); any other active disease; or who were either pregnant or planning pregnancy were excluded.

Study Design

This was a randomized, multicenter, double-blind, parallel-group, placebo-controlled, phase 3 clinical trial (NCT01281839), conducted between January 2011 and January 2013. Institutional review boards of all participating institutions approved the study and written informed consent was obtained from all participants according to local regulations. All authors had access to the study data, critically reviewed the manuscript at each draft, and approved the final draft for submission.

After stratification by HCV 1 subtype (1a, 1b, and other) and *IL28B* genotype (rs12979860; CC, CT, or TT), participants were randomized centrally in a 2:1 ratio to receive either simeprevir (150 mg once daily) plus PegIFNα-2a/RBV (180 μg/wk and 1000 or 1200 mg/day depending on body weight, respectively) (PR) for 12 weeks followed by RGT with PR alone for 12 or 36 weeks, or placebo with PR for 12 weeks followed by PR alone for 36 weeks (Supplementary Figure 1). Patients, study personnel, and the sponsor were blinded to the treatment groups. According to RGT criteria, PR therapy was completed at week 24 in simeprevir-treated patients with HCV-RNA levels less than 25 IU/mL at week 4 and undetectable levels at week 12. For patients not meeting these criteria and all patients in the placebo group, treatment with PR was continued until week 48. Patients in both groups were followed-up for 72 weeks after treatment initiation.

According to virologic stopping rules, simeprevir/placebo was discontinued if HCV-RNA level was greater than 1000 IU/mL at week 4. PR also was discontinued if the reduction in HCV RNA compared with baseline was less than 2 $\log_{10}$ IU/mL at week 12, or if HCV RNA was 25 IU/mL or greater at week 24 or 36. Investigators were formally blinded to HCV-RNA data until week 48 and to treatment group until week 72. An external HCV-RNA monitor (who was unblinded to treatment and to HCV-RNA measurements results) informed the investigator if a virologic stopping rule or the RGT criteria were met.

Assessments

Plasma HCV RNA was determined using the Roche COBAS TaqMan HCV/HPS assay version 2.0 (Roche Molecular Diagnostics, Pleasanton, CA). Standard population-based sequencing of the HCV NS3/4A protease domain was performed on baseline samples to determine the presence of naturally occurring baseline polymorphisms, including Q80K, and those from selected time points (based on HCV-RNA changes).

Standard HCV genotyping assays, the Siemens Versant HCV LiPA v2 assay (Siemens Healthcare Diagnostics, Tarrytown, NY) or, if that failed, the Trugene 5′NC genotyping assay, were used