LIVER, PANCREAS, AND BILIARY TRACT

Boceprevir With Peginterferon Alfa-2a–Ribavirin Is Effective for Previously Treated Chronic Hepatitis C Genotype 1 Infection

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This article has an accompanying continuing medical education activity on page e5. Learning Objectives—At the end of this activity, the successful learner will be able to apply data to treat previously treated patients with HCV genotype 1 with peginterferon alfa-2a–ribavirin and boceprevir.

BACKGROUND & AIMS: The addition of boceprevir to therapy with peginterferon alfa-2b and ribavirin results in significantly higher rates of sustained virologic response (SVR) in previously treated patients with chronic hepatitis C virus (HCV) genotype-1 infection, compared with peginterferon alfa-2b and ribavirin alone. We assessed SVR with boceprevir plus peginterferon alfa-2a–ribavirin (PEG2a/R) in patients with identical study entry criteria. **METHODS:** In a double-blind, placebo-controlled trial, 201 patients with HCV genotype-1 who had relapsed or not responded to previous therapy were assigned to groups (1:2) and given a 4-week lead-in phase of PEG2a/R, followed by placebo plus PEG2a/R for 44 weeks (PEG2a/R) or boceprevir plus PEG2a/R for 44 weeks (BOC/PEG2a/R). The primary end point was SVR 24 weeks after therapy ended. **RESULTS:** The addition of boceprevir after 4 weeks of lead-in therapy with PEG2a/R significantly increased the rate of SVR from 21% in the PEG2a/R group to 64% in the BOC/PEG2a/R group ($P < .0001$). Among patients with poor response to interferon therapy (<1-$\log_{10}$ decline in HCV RNA at week 4), 39% in the BOC/PEG2a/R group had SVRs, compared with none of the patients in the PEG2a/R group. Among patients with good response to interferon (≥1-$\log_{10}$ decline), 71% in the BOC/PEG2a/R group had SVRs, compared with 25% in the PEG2a/R group. A ≥1-$\log_{10}$ decline in HCV RNA at treatment week 4 was the strongest independent predictor of SVR, exceeding that of *IL-28B* genotype. Among 8 patients who began the study with HCV amino acid variants associated with boceprevir resistance, 3 (38%) achieved SVRs. Fifty percent of patients in the BOC/PEG2a/R group developed anemia (hemoglobin <10.0 g/dL), compared with 27% in the PEG2a/R group; 43% vs 21%, respectively, developed neutropenia (neutrophil count <750/mm^3). **CONCLUSIONS: The addition of boceprevir after 4 weeks of lead-in therapy with PEG2a/R caused significantly higher rates of SVR in previously treated patients with chronic HCV genotype-1 infection, compared with patients given only PEG2a/R. ClinicalTrials.gov Identifier: NCT00845065.**

Keywords: Protease Inhibitor; Antiviral Therapy; Clinical Trial; Liver Disease.

Hepatitis C virus (HCV) genotype-1 is the most common genotype in the United States, Europe, and many other countries and is the most difficult to eradicate with peginterferon/ribavirin therapy. With peginterferon alfa-2a (PEG2a) or alfa-2b and ribavirin (R) treatment, less than 50% of treatment-naive genotype-1 patients achieve sustained virologic response (SVR).[1,2] Compared with treatment-naive patients, response rates are even lower for genotype-1 nonresponders to previous interferon-ribavirin therapy, who are retreated with peginterferon-ribavirin.[3–6]

Boceprevir (BOC) is a peptidomimetic ketoamide protease inhibitor that binds reversibly to the HCV-NS3 active site. In phase 2 and 3 studies, addition of boceprevir to peginterferon alfa-2b–ribavirin in previously untreated (SPRINT-1 and 2)[7,8] and previous treatment-failure (RESPOND-2)[9] patients with HCV genotype-1 resulted in significantly higher rates of SVR as compared with peginterferon alfa-2b–ribavirin alone. In the RESPOND-2 trial, the rate of SVR was significantly higher in the 48-week boceprevir arm (66%) than in the control arm (21%, $P < .0001$).[9] Because of the widespread use of both peginterferon alfa-2b and alfa-2a in the treatment of HCV, this phase 3 study was designed to investigate the efficacy and safety of boceprevir when added to PEG2a/R backbone therapy in a patient population who met identical entry criteria as the RESPOND-2

Abbreviations used in this paper: AE, adverse event; BOC, boceprevir; BOC/PEG2a/R, boceprevir plus peginterferon alfa-2a–ribavirin; CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio; PEG2a, peginterferon alfa-2a; R, ribavirin; RAV, resistant associated variants; SVR, sustained virologic response.

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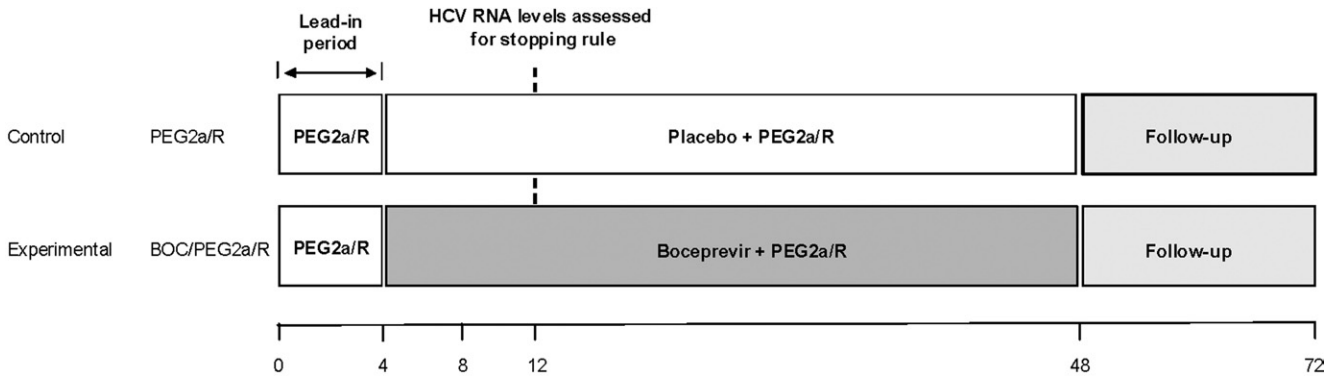

Figure 1. Study design.

trial that used peginterferon alfa-2b, that is, in adults with chronic HCV genotype-1 with previously demonstrated responsiveness to peginterferon and ribavirin but with failure to achieve SVR.

Methods

Patients

From February 23, 2009, to June 22, 2009, 201 patients with HCV genotype-1 were screened from 53 sites in North America and Europe. Eligible patients met identical entry criteria as the RESPOND-2 trial.[9] Eligibility criteria included demonstrated responsiveness to interferon (minimum duration of therapy of 12 weeks). We defined patients as having either nonresponse (ie, a decrease in the HCV RNA level of at least 2 $\log_{10}$ IU/mL by week 12 but with a detectable HCV RNA level during the therapy period) or relapse (ie, an undetectable HCV RNA level at the end of treatment, without subsequent attainment of SVR). Eligibility criteria included an absolute neutrophil count $\geq$1500/mm^3 ($\geq$1200/mm^3 for black patients), a platelet count $\geq$100,000/mm^3, and hemoglobin levels $\geq$12 g/dL for female patients and $\geq$13 g/dL for male patients. Exclusion criteria included hepatitis B or human immunodeficiency virus infection, any other cause of significant liver disease, decompensated liver disease, uncontrolled diabetes mellitus, severe psychiatric disorders, and/or active substance abuse. Pretreatment liver biopsy specimens were assessed for Metavir fibrosis scores and steatosis scores by a single pathologist who was unaware of the assignment of boceprevir or placebo.[9]

Study Design

The primary objective was to compare the rates of SVR achieved by using boceprevir in combination with open-label PEG2a (Pegasys; Hoffman-La Roche Ltd, Basle, Switzerland) and ribavirin with PEG2a/R plus placebo in adults with chronic HCV genotype-1 with previously demonstrated responsiveness to peginterferon and ribavirin but with failure to achieve SVR. The study was conducted in accordance with principles of good clinical practice and was approved by the appropriate institutional review boards and regulatory agencies. Informed consent was obtained from each patient. All authors had access to the study data and have reviewed and approved the final manuscript.

Patients were randomized in a 1:2 ratio by using an interactive voice response system with stratification by previous response to therapy (nonresponder or relapser) and HCV genotype (1a or 1b) as determined by Trugene HCV 5'NC (Bayer Healthcare, Tarrytown, NY) sequencing. Patients with HCV genotype-1 infection whose HCV subtype could not be classified were randomly assigned to one of the treatment groups. The HCV genotype-1 subtype was subsequently determined by means of sequencing of the nonstructural 5B (NS5B) region (Virco, Mechelen, Belgium).

PEG2a was administered subcutaneously at 180 μg once weekly. Ribavirin was administered by using weight-based dosing of 1000–1200 mg/d (divided daily dose). Boceprevir was administered orally at a dose of 800 mg 3 times daily (to be taken with food and with an interval of 7–9 hours between doses) in 4 capsules of 200 mg each. Placebo was matched to boceprevir. The study was double-blinded regarding the administration of boceprevir.

All patients received a 4-week lead-in with PEG2a/R (Figure 1). Subsequently, the control group received peginterferon alfa-2a–ribavirin plus placebo for 44 weeks (PEG2a/R group), and the second group received boceprevir plus PEG2a/R for 44 weeks (BOC/PEG2a/R group). HCV RNA levels were measured with the use of the TaqMan 2.0 assay (Roche Diagnostics, Indianapolis, IN), which had lower limits of quantification and detection of 25 and 9.3 IU/mL, respectively; the lower limit of detection was used for decision-making at various points throughout the study. Measurements were obtained at the screening visits and at baseline; every 2 weeks through week 12 and then weeks 16, 20, 24, 30, 36, 42, and 48; and follow-up weeks 4, 12, and 24. The stopping rule applied to both groups was failure to achieve an undetectable HCV RNA level at week 12, which resulted in discontinuation of all treatment and advancement to follow-up.

The study prospectively consented patients for pharmacogenomic testing and collected samples for biomarker identification. *IL-28B* genetic classification of patients was evaluated as a predictor of SVR by frequency tables and logistic regression models. *IL-28B* genotyping for markers rs12979860, rs12980275, and rs8103142 was performed by Gentris Clinical Genetics, Inc (Morrisville, NC) by using DNA Sanger sequencing technology. Several single nucleotide polymorphisms in linkage disequilibrium are in this region, and the principal one evaluated was the rs12979860 locus, as in other studies.[10,11] *IL-28B* was analyzed retrospectively.

Safety

Adverse events (AEs) were graded by investigators according to a modified World Health Organization grading