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CLINICAL—LIVER

ABT-450, Ritonavir, Ombitasvir, and Dasabuvir Achieves 97% and 100% Sustained Virologic Response With or Without Ribavirin in Treatment-Experienced Patients With HCV Genotype 1b Infection

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BACKGROUND & AIMS: The interferon-free regimen of ABT-450 (a protease inhibitor), ritonavir, ombitasvir (an NS5A inhibitor), dasabuvir (a non-nucleoside polymerase inhibitor), and ribavirin has shown efficacy in patients with hepatitis C virus (HCV) genotype 1b infection—the most prevalent subgenotype worldwide. We evaluated whether ribavirin is necessary for ABT-450, ritonavir, ombitasvir, and dasabuvir to produce high rates of sustained virologic response (SVR) in these patients. **METHODS:** We performed a multicenter, open-label, phase 3 trial of 179 patients with HCV genotype 1b infection, without cirrhosis, previously treated with peginterferon and ribavirin. Patients were assigned randomly (1:1) to groups given ABT-450, ritonavir, ombitasvir, and dasabuvir, with ribavirin (group 1) or without (group 2) for 12 weeks. The primary end point was SVR 12 weeks after treatment (SVR12). We assessed the noninferiority of this regimen to the rate of response reported (64%) for a similar population treated with telaprevir, peginterferon, and ribavirin. **RESULTS:** Groups 1 and 2 each had high rates of SVR12, which were noninferior to the reported rate of response to the combination of telaprevir, peginterferon, and ribavirin (group 1: 96.6%; 95% confidence interval, 92.8%–100%; and group 2: 100%; 95% confidence interval, 95.9%–100%). The rate of response in group 2 was noninferior to that of group 1. No virologic failure occurred during the study. Two patients (1.1%) discontinued the study owing to adverse events, both in group 1. The most common adverse events in groups 1 and 2 were fatigue (31.9% vs 15.8%) and headache (24.2% vs 23.2%), respectively. Decreases in hemoglobin level to less than the lower limit of normal were more frequent in group 1 (42.0% vs 5.5% in group 2; $P < .001$), although only 2 patients had hemoglobin levels less than 10 g/dL. **CONCLUSIONS:** The interferon-free regimen of ABT-450, ritonavir, ombitasvir, and dasabuvir, with or without ribavirin, produces a high rate of SVR12 in treatment-experienced patients with HCV genotype 1b infection. Both regimens are well tolerated, as shown by the low rate of discontinuations and generally mild adverse events. ClinicalTrials.gov number: NCT01674725

Keywords: PEARL-II; Ribavirin-Free; IFN; Interferon-Free Therapy.

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Untreated chronic hepatitis C virus (HCV) infection is a leading cause of liver damage, cirrhosis, and hepatocellular carcinoma.[1] The prevalence of HCV infection is estimated to be 3% worldwide and results in approximately 350, 000 deaths annually.[2,3] Genotype 1 accounts for approximately 70% of all HCV infections and subgenotype 1b is most predominant in Europe and Eastern Asia. Approved direct-acting antiviral agents (DAAs), telaprevir, boceprevir, sofosbuvir, and simeprevir, given with peginterferon (pegIFN) and ribavirin (RBV), have reported sustained virologic response (SVR) rates of 67%–89% in HCV genotype 1–infected patients. Response rates with DAA regimens are generally lower in patients who have failed previous pegIFN-containing treatment regimens than in treatment-naive

Abbreviations used in this paper: **AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DAA, direct-acting antiviral agent; HCV, hepatitis C virus; pegIFN, peginterferon; RBV, ribavirin; RT-PCR, reverse-transcription polymerase chain reaction; SVR, sustained virologic response; SVR12, sustained virologic response 12 weeks after treatment; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.**

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patients, and are noticeably lower among prior null responders.[4–8] In addition, the toxicity of pegIFN and long duration of therapy (up to 48 weeks with some regimens) are a hardship for patients.[9] Notably, pegIFN-based treatment regimens have well-documented adverse event (AE) profiles including influenza-like symptoms and depression, which have led to unfavorable discontinuation rates in clinical trials,[6,9–12] and RBV also has associated side effects including teratogenicity, hemolytic anemia, and rash.[13,14]

All-oral and interferon-free HCV treatment regimens with DAAs provide wider treatment access to patients in need with chronic liver disease. ABT-450 is an NS3/4A protease inhibitor with in vitro nanomolar antiviral activity and is co-dosed with the CYP3A4 inhibitor, ritonavir, which significantly increases peak and trough drug concentrations, enabling once-daily dosing.[15] The multitargeted, all-oral combination of the 3 DAAs of ABT-450/ritonavir, ombitasvir (formerly ABT-267), an HCV NS5A inhibitor with pangenotypic picomolar antiviral activity,[16] and dasabuvir (formerly ABT-333), an HCV NS5B RNA non-nucleoside polymerase inhibitor, with RBV was shown in a phase 2b trial to achieve high rates of SVR 12 weeks post-treatment (SVR12) in treatment-naive and treatment-experienced genotype 1–infected patients. With this regimen, a 93% SVR12 rate was achieved in genotype 1–infected noncirrhotic patients with prior null response to pegIFN/RBV, and a 100% SVR12 rate was achieved in the genotype 1b patient subset.[17] These high response rates in prior null responders, considered difficult to cure, are promising and require confirmation in a large phase 3 trial. Although ABT-450/ritonavir/ombitasvir and dasabuvir with RBV may achieve high SVR12 rates, determining the benefit gained by including RBV in the regimen has not been assessed in these patients. This phase 3 study (PEARL-II) evaluated the efficacy and safety of 12 weeks of treatment with coformulated ABT-450/ritonavir/ombitasvir and dasabuvir with or without RBV exclusively in noncirrhotic pegIFN/RBV treatment-experienced HCV genotype 1b–infected patients.

Materials and Methods

Patients

Adults were age 18–70 years at the time of screening from 43 sites in Austria, Belgium, Italy, The Netherlands, Portugal, Puerto Rico, Sweden, Switzerland, Turkey, and the United States. Patients were required to have documentation that they previously failed treatment with pegIFN/RBV. Eligible patients were required to be noncirrhotic with chronic HCV genotype 1b infection for at least 6 months with an HCV-RNA level greater than 10, 000 IU/mL at screening. Patients were excluded if they had evidence of co-infection with any HCV genotype other than 1b or tested positive for hepatitis B surface antigen or anti–human immunodeficiency virus antibody at screening. Detailed eligibility criteria are provided in the Supplementary Appendix.

Study Design

Patients were stratified by type of previous nonresponse to pegIFN/RBV treatment (null responders, partial responders, and relapsers) and randomized 1:1 to receive the 12-week regimen of coformulated ABT-450/ritonavir/ombitasvir (150/100/25 mg once daily) and dasabuvir (250 mg twice daily) with either weight-based RBV dosed twice daily (1000 mg daily if body weight $<$ 75 kg, 1200 mg daily if body weight was $\geq$ 75 kg) for group 1 or without RBV for group 2 (Supplementary Figure 1). After 12 weeks of treatment, patients were followed up for an 48 additional weeks. Additional details on study design are in the Supplementary Appendix.

The study was conducted in accordance with the International Conference of Harmonisation guidelines, applicable regulations, and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. All patients provided written informed consent. All authors had access to relevant data, and critically reviewed, revised, and approved the manuscript.

Safety Assessments

Adverse event assessments were reported from the time of study drug administration until 30 days after the last dose and were judged as mild, moderate, or severe; clinical laboratory testing was performed at each study visit. Serious AEs were recorded throughout the study.

Efficacy End Points

Plasma samples were collected at screening and at each study visit and HCV-RNA levels were determined using the Roche COBAS TaqMan real-time reverse-transcription polymerase chain reaction assay v2.0 (Roche Molecular Diagnostics, Pleasanton, CA) at a central laboratory. A fixed-sequence testing procedure was used to control type I error at 0.05. The primary efficacy end point was noninferiority of the SVR12 rates (assessed by HCV-RNA level $<$ 25 IU/mL) in group 2 and group 1 to the historical SVR12 rate for telaprevir plus pegIFN/RBV in HCV genotype 1b–infected patients who were relapsers, partial responders, or null responders to previous pegIFN/RBV treatment,[4] adjusted for noncirrhotic patients in this study. Group 1 and group 2 noninferiority could be claimed if the SVR12 lower limit of the 95% confidence interval (CI) was greater than the upper limit of the CI for the historical rate minus a 10.5% noninferiority margin (64%). Further details of historical noninferiority calculations are provided in the Supplementary Appendix. Secondary efficacy end points in the fixed sequence included the following: (1) comparison of the percentage of patients with a decrease in hemoglobin level to less than the lower limit of normal at the end of treatment; (2) superiority of group 1 and group 2 to the historical rate for telaprevir plus pegIFN/RBV (75%); and (3) noninferiority of group 2 to group 1 using a 10.5% noninferiority margin for the SVR12 difference. The percentage of patients with on-treatment virologic failure and post-treatment relapse also was assessed.

Virologic Failure Criteria

Virologic failure leading to discontinuation of study drug was determined if the following criteria occurred: confirmed increase from nadir in HCV-RNA level (defined as 2 consecutive HCV-RNA measurements greater than 1 $\log_{10}$ IU/mL greater than nadir) at any point during treatment; failure to achieve HCV-RNA level less than 25 IU/mL by week 6; and confirmed HCV-RNA level of 25 IU/mL or greater in 2 consecutive measurements at any point during treatment after HCV-RNA level