Research Article

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Safety and efficacy of boceprevir/peginterferon/ribavirin for HCV G1 compensated cirrhotics: Meta-analysis of 5 trials

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Background & Aims: HCV-infected cirrhotics may urgently need therapy but are often under-represented in clinical trials resulting in limited data to guide their management. We performed a meta-analysis of well-compensated cirrhotic patients from five Phase 3 trials.

Methods: Patients received P/R (peginterferon/ribavirin; 4 weeks) followed by BOC (boceprevir)/P/R or P/R for 24, 32, or 44 weeks. Sustained virologic response (SVR) rates were calculated by Metavir score. Multivariate logistic regression (MLR) models identified baseline and on-treatment predictors of SVR. Safety was evaluated by adverse-event (AE) reporting and laboratory monitoring.

Results: Pooled meta-estimates for SVR rates (95% confidence interval) in 212 F4 (cirrhotic) patients were 55% (43, 66) with BOC/P/R *vs.*17% (0, 41) with P/R. MLR identified 4 predictors of SVR in F3/F4 patients: undetectable HCV-RNA at treatment week (TW) 8; $\geqslant$1 $\log_{10}$ decline in HCV-RNA from baseline at TW4; male; and baseline HCV-RNA $\leqslant$800,000 IU/ml. SVR rate was 89% (65/73) in F4 patients who were HCV-RNA undetectable at TW8. No F3 (0/5) or F4 (0/17) patients with <3 $\log_{10}$ decline and detectable HCV-RNA at TW8 achieved SVR. Anemia and diarrhea occurred more frequently in cirrhotic than non-cirrhotic patients. Serious AEs, discontinuations due to an AE, interventions to manage anemia, infections, and thrombocytopenia occurred more frequently in cirrhotics with BOC/P/R than P/R. Potential hepatic decompensation and/or sepsis were identified in 2 P/R and 3 BOC/P/R recipients.

Conclusions: BOC/P/R appears to have a generally favorable benefit-risk profile in compensated cirrhotic patients. SVR rates were particularly high in cirrhotic patients with undetectable HCV-RNA at TW8.

Introduction

Cirrhotic patients with chronic hepatitis C continue to present a therapeutic challenge in the era of directly acting antiviral agents because of lower SVR rates and poorer tolerability of therapy compared with non-cirrhotics [1]. Yet there is a clear benefit in treating cirrhotics and in many cirrhotics, an urgency to treat before patients advance to decompensated cirrhosis at which point interferon-based antiviral therapies are contraindicated. Initial experience with BOC/P/R was obtained in the two pivotal Phase 3 trials; the SVR rates in 79 cirrhotics ranged from 31% to 77% and safety was similar compared to patients with mild to moderate fibrosis [2]. An additional perspective was provided by the CUPIC study, which evaluated triple combination regimens with either telaprevir or BOC in a wider range of treatment-experienced cirrhotic patients (many of whom would not have qualified for pivotal trials) [3]. The SVR rate in CUPIC at 12 weeks after end of therapy with BOC/P/R was 41% (79/190) [4]. However, the safety profile in CUPIC differed from the pivotal trial experience and both regimens with boceprevir or telaprevir were poorly tolerated, especially in those subjects with low platelet counts and albumin levels at baseline.

The ultimate goal of this analysis was to understand the overall risk to benefit ratio of BOC/P/R treatment in well-compensated cirrhotic patients using expanded data from 5 Phase 3 clinical

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Abbreviations: HCV, hepatitis C virus; BOC, boceprevir; P/R, peginterferon/ribavirin; SVR, sustained virologic response; MLR, multivariate logistic regression; AE, adverse event; TW, treatment week; SAE, serious adverse event; CI, confidence interval.

trials. Specifically, we sought to identify baseline and on-treatment variables that could help to predict response and to guide clinical decisions about BOC/P/R therapy for cirrhotic patients, including decisions about discontinuation for futility (low likelihood of achieving SVR) and decisions regarding the duration of treatment. We examined efficacy and safety in the cirrhotic population. We also evaluated potential early stopping rules (at weeks 4 and 8) as well as the utility of response-guided paradigms to potentially shorten duration of therapy to <48 weeks in carefully selected patients.

Materials and methods

Objectives

The primary objectives of this retrospective study were to estimate the SVR rate and adverse-event profile for BOC (VICTRELIS® (boceprevir), Merck & Co., Inc., Whitehouse Station, NJ, USA) plus P/R in compensated cirrhotic (Metavir fibrosis score F4) patients with chronic hepatitis C genotype 1 infection based on pooled data from 5 Phase 3 clinical studies (P05101 [RESPOND-2 [5]], P05216 [SPRINT-2 [6]], P05514 [PROVIDE; [7]], P05685 [Peginterferon alfa-2a Study [8]], and P06086 [Anemia Management Study; [9]] (Supplementary Table 1).

ClinicalTrials.gov Identifiers: NCT00708500, NCT00705432, NCT01023035, NCT00845065, NCT00910624.

Assessment of cirrhosis

Cirrhosis was determined by liver biopsies performed on all patients and centrally read by a single pathologist. Cirrhosis was defined as Metavir score F4; advanced fibrosis without cirrhosis as Metavir score F3.

Statistical analysis plan

The pooled analysis was conducted using individual participant data from 5 clinical studies (P05101, P05216, P05514, P05685, and P06086) with a total number of 2522 patients. No formal hypothesis-testing or multiplicity adjustments were planned.

Efficacy analyses

The primary efficacy analysis was conducted on the pooled patients from the BOC/P/R arms who received $\geqslant 1$ dose of any study medication and who were fibrosis score F4 (cirrhotics), F3 or F0–F2. An SVR was defined as having undetectable HCV-RNA ("Target Not Detected" or "HCV-RNA Not Detected") in the plasma 24 weeks after completion or discontinuation of therapy. HCV-RNA was measured using a Roche COBAS® TaqMan® assay with a lower limit of detection of 9.3 IU/ml. Meta-analysis methods were used to estimate the SVR rate for the primary analysis in the pooled cirrhotic patients as well as for pooled F0–F2 and F3 patients treated with BOC/P/R.

The relationship between baseline factors and SVR for patients receiving BOC/P/R with different fibrosis scores (F0–F2, F3/F4) was explored using multivariate logistic regression analysis. The multivariate logistic regression analysis was performed on pooled F3 and F4 patients in order increase the power to identify additional predictors of SVR.

Safety analyses

For all safety analyses, the results from all patients who received $\geqslant 1$ dose of any study medication were analyzed by treatment (BOC/P/R *vs.* P/R) and fibrosis score (F0/F1/F2, F3, and F4). The numbers of patients reporting any AEs and serious AEs (SAEs; including deaths and hospitalizations), and AEs leading to study drug discontinuations were tabulated. Laboratory assessments during treatment focused on anemia, neutropenia, and thrombocytopenia. The following parameters were considered to potentially represent hepatic decompensation: new onset of ascites, encephalopathy, bleeding esophageal varices, jaundice, sepsis (in the context of declining liver function); increase in bilirubin (total >4.0 with at least 50% direct), or prothrombin time >10% above laboratory reference range [10,11]. Patients with the above findings, regardless of the Metavir classification, were adjudicated by John Vierling and Savino Bruno who were blinded to the treatment regimen and Metavir score.

Results

Patient accounting and baseline characteristics

The distributions of patients according to treatment (BOC/P/R *vs.* P/R) and fibrosis scores in the pooled data are presented in Supplementary Table 1. Eighty percent (1925/2415) of patients came from the BOC/P/R arms of the 5 studies, and 20% (490/2415) of patients came from the P/R arms of 3 studies (P05101, P05216, and P05685; no P/R arms were included in P05514 and P06086). Fibrosis scores were distributed as: F0/F1/F2, 86% (2074/2415); F3, 5% (129/2415); and F4, 9% (212/2415). Of the 212 F4 patients, 32 (15%) patients received P/R and 180 (85%) received BOC/P/R. The number of patients, prior treatment history (treatment naïve or previous treatment failure), and treatment assignments (P/R, BOC/P/R for 48 weeks, and Response Guided Therapy [RGT] for BOC/P/R if applicable) from each study, as well as fibrosis scores by treatment assignment, are provided in Supplementary Table 2.

Baseline characteristics are shown in Table 1. F4 patients treated with BOC/P/R were approximately 53 yr (compared to 50 yr for F0–F2 patients), 62% male, 83% White, 10% Black, with a mean body mass index of 29.8 (compared to 28 for F0–F2). Approximately 51% of F4 patients treated with BOC/P/R were infected with HCV subtype 1a. In F4 patients, mean platelet count was 166×10^9/L (compared to approximately 250×10^9/L for F0–F2 patients), 44% had mean platelet counts $<150 \times 10^9$/L (compared to 6% of F0–F2 patients), and 12% had serum albumin levels <35 g/L (compared to 2% of F0–F2 patients).

SVR rates

A meta-analysis was performed in order to estimate the SVR rates according to pooled data by fibrosis score (Fig. 1A; Supplementary Figs. S1 and S2). The meta-estimates of the SVR rates were 55% (95% confidence interval [CI]: 43, 66) *vs.* 17% (95% CI: 0, 41) for F4 patients treated with BOC/P/R or P/R, respectively (preliminary results were presented at EASL [12]). Among patients treated with BOC/P/R, the meta-estimates for the SVR rates were comparable in F4 (55%) and F3 patients (54%; 95% CI: 45, 64) and were numerically lower than the SVR rates in F0–F2 (66%; 95% CI: 63, 68) patients.

Several factors that predicted achievement of an SVR in F3/F4 patients were identified with multivariate logistic regression models. Undetectable HCV-RNA at treatment week 8, a $\geqslant 1 \log_{10}$ decline from baseline in HCV-RNA at treatment week 4, low baseline viral load ($\leqslant$800,000 IU/ml), and male gender were significant factors that predicted SVR in F3/F4 patients (Fig. 3; Supplementary Table 3). The most significant factor for achieving an SVR was undetectable HCV-RNA at treatment week 8 in F3 and F4 patients. In F0–F2 patients, undetectable HCV-RNA at treatment week 8, a $\geqslant 1 \log_{10}$ decline from baseline in HCV-RNA at treatment week 4, non-black and HCV subtype 1b were significant predictors of SVR (Supplementary Table 4). If achievement of an SVR was analyzed by multivariate logistic regression in only F4 patients, then only low undetectable HCV-RNA at treatment week 8 (odds ratio = 10.90; p value <0.0001) and a