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Original Article

Boceprevir-based triple therapy to rescue HCV genotype 1/HBV dually infected patients refractory to peginterferon plus ribavirin combination therapy in Taiwan

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Background/purpose: The role of directly-acting antivirals (DAA)-containing regimens in the treatment of patients dually-infected with hepatitis C virus (HCV) and hepatitis B virus (HBV) remains unclear. The pilot study aimed to explore the safety and efficacy of a protease inhibitor, boceprevir, in combination with peginterferon/ribavirin for HCV genotype 1 (HCV-1)/HBV dually-infected patients refractory to prior peginterferon/ribavirin.

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Methods: Twelve peginterferon-experienced patients dually-infected with HCV-1/HBV were assigned to receive boceprevir 800 mg, twice a day, plus peginterferon-α 2b 1.5 μg/kg/week and ribavirin 800-1400 mg/day for 36 or 48 weeks. The primary endpoint was HCV sustained virological response (SVR, HCV RNA undetectable 24 weeks after end-of-treatment).
Results: Five patients terminated treatment early due to adverse events (one at week 4, one at week 46), virological failures (one non-response and one breakthrough), and patient request (n = 1). Eight patients achieved HCV SVR (66.7% in full-analysis set and 72.7% in modified intention-to-treat population). The HCV SVR rate was 71.4% (5/7) in prior relapsers, 60.0% (3/5) in prior null responder; 75% in non-cirrhotic and 50% in cirrhotic patients. All four patients of prior non-cirrhotic relapsers received 36-week regimen and achieved HCV SVR. There was no HBV-related hepatic flare. All patients experienced at least one adverse event. Two had serious adverse events.
Conclusion: Boceprevir plus peginterferon/ribavirin is effective in the treatment of HCV-1/HBV dually infected patients' refractory to prior peginterferon/ribavirin combination therapy.

Introduction

Chronic viral hepatitis is an important public health issue, which frequent leads to liver cirrhosis, hepatocellular carcinoma (HCC) and liver-related death.[1,2] Around 340 to 400 million persons are infected with hepatitis B virus (HBV) and 130 to 210 million persons are infected with hepatitis C virus (HCV) worldwide.[3,4] In Taiwan, the prevalence of HBV infection is 15—20%, and the prevalence of HCV infection is 2—5% in general population.[5,6] Moreover, there are HCV-hyperendemic areas in southern Taiwan with anti-HCV prevalence rate of as high as 30—40%.[5] Therefore, HBV/HCV dual infections is not uncommon in HBV epidemic areas, such as Southeastern Asia[7] and Taiwan with a prevalence rate of 1.1%.[5] Recent study showed that the risk of HCC incidence is even higher among HBV/HCV co-infected patients than those with HBV or HCV mono-infection,[8] indicating the importance of disease control in this clinical setting.

The interferon (IFN) and ribavirin (RBV) combination therapy has been effective in the treatment of HCV-dominant, treatment-naïve patients with HCV/HBV dual infections.[7,9—11] In 2009, peginterferon (PEG-IFN) plus RBV was shown to be effective in the treatment of HCV/HBV co-infected patients with 48 weeks of PEG-IFN/RBV for HCV genotype 1(HCV GT1)/HBV dually-infected patients, the HCV sustained virological response (SVR) rate could achieve 72%, which was comparable to 77% for patients with HCV GT1 mono-infection.[12] More recently, we demonstrated that response-guided therapy with tailored regimen of PEG-IFN/RBV could provide comparable SVR rate to the genotype-guided therapy for HCV/HBV dually-infected patients.[13] Furthermore, PEG-IFN/RBV for HCV/HBV co-infection could enhance seroclearance of hepatitis B surface antigen (HBsAg) with an HBsAg loss rate of 11%,[12,14] and up to 30.0% during a 5-year follow up period.[15] Nevertheless, there is about 30% of HCV GT1/HBV co-infected patients refractory to PEG-IFN/RBV,[12] which remains at high risk of HCC and liver-related death.

For HCV GT1 mono-infected patients who refractory to previous PEG-IFN plus RBV combination therapy, boceprevir plus PEG-IFN/RBV triple therapy can improve the treatment efficacy, about 3 times when compared to those with PEG-IFN/RBV dual therapy.[16] Therefore, the current study hypothesized that adding boceprevir to PEG-IFN/RBV as triple therapy might be effective in the treatment of HCV-1/HBV dually-infected patients who failed to previous Peg-IFN/RBV dual therapy. This pilot study aimed to prove the concept and to explore the safety and efficacy of boceprevir-based triple therapy to rescue HCV GT1/HBV dually-infected Taiwanese patients refractory to prior PEG-IFN/RBV.

Methods

Subjects

Twelve eligible patients from Kaohsiung Medical University Hospital and National Taiwan University Hospital were enrolled in the study from 12 August 2014 to 28 June 2016. The key inclusion criteria were: 1) 20 years or older; 2) HCV GT1/HBV dual infections with HCV dominance, defined as seropositive for HCV RNA GT1, antibodies to HCV (anti-HCV) positive and HBsAg, and seronegative for hepatitis B e antigen (HBeAg); 3) history of refractory to prior PEG-IFN/RBV treatment for at least 12 weeks; 4) compensated liver disease consistent with chronic hepatitis C and/or B, without other etiology, 5) patient met all of the indications and none of the contra-indications for treatment with PEG-IFN alpha-2b/RBV and boceprevir defined in the labels for the PEG-IFN/RBV to be used in combination with boceprevir. The key exclusion criteria were mixed genotypes including HCV genotype other than genotype 1, history of receiving boceprevir, telaprevir, or any other HCV protease inhibitor treatment, history or evidence of decompensated liver disease, organ transplant, co-infected with human immunodeficiency virus (HIV), and other serious illness, including malignancy, active coronary artery disease or cardiac

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