Research Article

JOURNAL OF HEPATOLOGY

Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine

Jacob Lalezari[1,*], J. Greg Sullivan[2], Peter Varunok[3], Edward Galen[4], Kris V. Kowdley[5], Vinod Rustgi[6], Humberto Aguilar[7], Franco Felizarta[8], Barbara McGovern[9], Martin King[9], Akshanth R. Polepally[9], Daniel E. Cohen[9]

[1]*Quest Clinical Research, San Francisco, CA, United States;* [2]*Parkway Medical Center, Birmingham, AL, United States;* [3]*Premier Medical Group of the Hudson Valley, PC, Poughkeepsie, NY, United States;* [4]*Northwest Gastroenterology Clinic, Portland, OR, United States;* [5]*Digestive Disease Institute, Virginia Mason Medical Center, Seattle, WA, United States;* [6]*Thomas E. Starzl Transplantation Institute, UPMC Montefiore, Pittsburgh, PA, United States;* [7]*Louisiana Research Center, LLC, Shreveport, LA, United States;* [8]*Private Practice, Bakersfield, CA, United States;* [9]*AbbVie Inc., North Chicago, IL, United States*

Background & Aims: Hepatitis C virus (HCV)-infected patients with a history of injection drug use have low rates of initiation and completion of interferon-based therapies. This study evaluated efficacy, safety, and pharmacokinetics of a 12-week all-oral regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir + ribavirin in HCV genotype 1-infected patients on stable opioid replacement therapy.

Methods: This was a phase II, multicenter, open-label, single-arm study in treatment-naïve or peginterferon/ribavirin treatment-experienced HCV genotype 1-infected patients on methadone or buprenorphine ± naloxone. Patients received 12 weeks of co-formulated ombitasvir/paritaprevir/ritonavir (25 mg/150 mg/100 mg once daily) and dasabuvir (250 mg twice daily) + weight-based ribavirin. The primary efficacy endpoint was sustained virologic response 12 weeks post-treatment.

Results: Thirty-eight non-cirrhotic patients on chronic methadone (n = 19) or buprenorphine (n = 19) were enrolled. A total of 37 patients (97.4%) had a sustained virologic response 12 weeks post-treatment. No patient had a viral breakthrough or relapse. One patient discontinued due to serious adverse events unrelated to study drug (cerebrovascular accident and sarcoma). The most frequent adverse events were nausea, fatigue, and headache. Eight patients had on-treatment hemoglobin concentrations <10 g/dl. Pharmacokinetic analyses indicated no clinically meaningful impact of methadone or buprenorphine on ombitasvir, paritaprevir, ritonavir, dasabuvir, or dasabuvir M1 metabolite exposures. No dose adjustments of methadone or buprenorphine were required.

Conclusions: The interferon-free regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir + ribavirin for 12 weeks was well tolerated and achieved sustained virologic response in 97.4% of patients on opioid substitution therapy in this study. This all-oral regimen may provide an effective alternative to interferon-based therapies for HCV-infected patients with a history of injection drug use.

Keywords: Hepatitis C virus; Interferon-free therapy; Sustained virologic response; Opioid replacement therapy; People who inject drugs.

Received 19 September 2014; received in revised form 17 March 2015; accepted 25 March 2015; available online 1 April 2015

* Corresponding author. Address: Quest Clinical Research, 2300 Sutter St. Suite 202, San Francisco, CA 94115, United States. Tel.: +1 415 353 0800; fax: +1 415 353 0801.

E-mail address: drjay@questclinical.com (J. Lalezari).

Abbreviations: HCV, hepatitis C virus; CYP3A4, cytochrome P450 isoform 3A4; RNA, ribonucleic acid; HIV, human immunodeficiency virus; LLOD, lower limit of detection; LLOQ, lower limit of quantitation; MedDRA, Medical Dictionary for Regulatory Activities; MEMS, Medication Event Monitoring System; C_{max}, maximum observed plasma concentration; AUC, area under the plasma concentration-time curve; T_{max}, time to C_{max}; *IL28B*, interleukin-28B; EOTR, end of treatment response; SVR4, sustained virologic response 4 weeks post-treatment; SVR12, sustained virologic response 12 weeks post-treatment; SVR24, sustained virologic response 24 weeks post-treatment; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3.

Introduction

Injection drug use is the main source of hepatitis C virus (HCV) infections in industrialized nations [1]. Worldwide, approximately 10 million people who inject drugs (PWID) have been infected [2], with a global prevalence among long-term injection drug users of 64–94% [3,4]. Compounding this problem, rates of treatment initiation for HCV-infected PWID have been reported to be under 10% [5–7]. Among the small portion of PWID who do initiate treatment, response rates are limited by a high frequency of discontinuation related to interferon toxicity [8–13]. Thus, interferon-free regimens of direct-acting antivirals with improved efficacy and tolerability may be crucial in increasing the rate of successful treatment in this population.

Paritaprevir (formerly ABT-450) is a NS3/4A protease inhibitor that was identified by AbbVie and Enanta as a lead compound for clinical development. Co-administration with ritonavir, an inhibitor of the cytochrome P-450 enzyme CYP3A4, increases the peak, trough, and overall plasma concentrations of

paritaprevir, resulting in high paritaprevir exposures with once daily dosing [14]. When administered with ritonavir to previously untreated genotype 1-infected patients, 3 days of paritaprevir monotherapy decreased mean plasma HCV RNA levels by approximately 4 $\log_{10}$ IU/ml [15]. Ombitasvir (formerly ABT-267) is a NS5A inhibitor; 3 days of ombitasvir monotherapy decreased mean HCV RNA levels by approximately 3 $\log_{10}$ IU/ml [16]. Ombitasvir, paritaprevir, and ritonavir have been co-formulated into a single fixed-dose tablet (ombitasvir/paritaprevir/r). Dasabuvir (formerly ABT-333) is a non-nucleoside NS5B polymerase inhibitor; 3 days of dasabuvir monotherapy decreased mean HCV RNA levels by approximately 1 $\log_{10}$ IU/ml [17].

The combination of these three direct-acting antiviral agents plus ribavirin was well tolerated in clinical trials, and resulted in high sustained virologic response rates in genotype 1-infected patients in the absence of exogenous interferon [18–20]. In phase III trials, 12 weeks of treatment with ombitasvir/paritaprevir/r and dasabuvir plus ribavirin resulted in sustained virologic response rates 12 weeks post-treatment of 96% in both previously untreated and treatment-experienced patients without cirrhosis [18,20]. One percent or less of patients in these trials discontinued treatment due to adverse events [18,20]. The study presented here examined the efficacy, safety, and pharmacokinetics of this multi-targeted regimen in HCV genotype 1-infected patients on chronic opioid replacement therapy with either methadone or buprenorphine.

Patients and methods

Patients

Patients were screened and enrolled at eight sites in the United States beginning in April 2013. Eligible patients were 18–70 years of age and had a body mass index $\geqslant$18 and <38 kg/m^2, chronic HCV genotype 1 infection, plasma HCV RNA >10,000 IU/ml, and absence of cirrhosis. Patients were treatment-naïve or peginterferon/ribavirin treatment-experienced, and on a stable opioid replacement therapy of methadone or buprenorphine ± naloxone for at least 6 months before screening. Patients had no evidence of HIV or hepatitis B coinfection and no liver disease due to causes other than HCV. All patients signed an informed consent form. The study was conducted in accordance with the protocol, International Conference on Harmonisation guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki.

Study design

This was a phase II, multicenter, open-label, single-arm study. All patients received ombitasvir/paritaprevir/r 25 mg/150 mg/100 mg once daily and dasabuvir 250 mg twice daily for 12 weeks. Ribavirin was dosed twice daily at 1000 mg total daily dose for patients <75 kg or 1200 mg total daily dose for patients $\geqslant$75 kg. Patients were followed for 48 weeks after the end of the treatment period. The study protocol was developed by the investigators and AbbVie. All authors had access to the data and participated in data analysis and preparation of the manuscript.

Efficacy assessments

Plasma HCV RNA levels were determined by a central laboratory using the Roche COBAS® TaqMan® real-time reverse transcriptase-polymerase chain reaction assay v2.0. The lower limit of detection (LLOD) of this assay is 15 IU/ml and the lower limit of quantitation (LLOQ) is 25 IU/ml. HCV genotype and subtype were assessed from a plasma sample collected at screening using the Versant® HCV Genotype Inno-LiPA Assay, version 2.0 (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY). Samples for HCV RNA measurement were collected at screening, study day 1, weeks 1, 2, 4, 6, 8, 10, and 12 (or end of treatment), and at post-treatment weeks 2, 4, 8, 12, 24, 36, and 48 (or discontinuation). Treatment was to be stopped if any of the following criteria were met: a confirmed HCV RNA increase from nadir at any time point during treatment, failure to achieve HCV RNA < LLOQ by week 6, or confirmed HCV RNA $\geqslant$ LLOQ at any point during treatment after HCV RNA < LLOQ.

Safety analyses

Adverse events were collected from the time of study drug administration until 30 days following the end of study drug administration. Serious adverse events were collected from the time of signing of the informed consent form through the end of the study. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The investigator assessed the severity of each adverse event and its relationship to the use of study drug. Clinical laboratory testing occurred at all treatment period visits and at post-treatment weeks 4 and 48, or at the time of study discontinuation.

Steady-state pharmacokinetic analyses

Blood samples for the determination of dasabuvir, dasabuvir M1 metabolite, ombitasvir, paritaprevir, ritonavir, and ribavirin concentrations were collected approximately 2, 4, 6, and 24 hours post-dosing at a visit at least 2 weeks after the start of treatment, from those patients who gave consent for intensive pharmacokinetic sampling. The Medication Event Monitoring System (MEMS) caps were used to obtain daily dosing histories for dasabuvir, ombitasvir/paritaprevir/ritonavir, and ribavirin for all patients. Plasma samples were processed and assayed according to validated bioanalytical methods. Plasma concentrations of dasabuvir, dasabuvir M1 metabolite, ombitasvir, paritaprevir, ritonavir, and ribavirin were determined using a validated liquid chromatography method with tandem mass spectrometric detection with LLOQ of 4.58, 4.77, 0.462, 0.601, 4.93, and 98.1 ng/ml, respectively. Individual blood concentrations of S-methadone, R-methadone, buprenorphine, norbuprenorphine, and naloxone were not measured.

Statistical assessments

The primary endpoint was the percentage of patients with sustained virologic response 12 weeks post-treatment, defined as HCV RNA < LLOQ 12 weeks after the last dose of study drugs. Secondary endpoints included the percentage of patients with virologic failure during treatment (confirmed HCV RNA $\geqslant$ LLOQ after HCV RNA < LLOQ during treatment or confirmed HCV RNA $\geqslant$ LLOQ at the end of treatment) and the percentage of patients with post-treatment relapse (confirmed HCV RNA $\geqslant$ LLOQ between end of treatment and 12 weeks after the last dose of study drugs among patients completing treatment with HCV RNA < LLOQ at the end of treatment). Additional efficacy endpoints included percentage of patients with end of treatment response, defined as HCV RNA < LLOQ at week 12, sustained virologic response 4 weeks post-treatment, and sustained virologic response 24 weeks post-treatment. All analyses were performed on all patients who enrolled and received at least one dose of study drugs. SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system was used for all analyses. All confidence intervals were 2-sided with an α level of 0.05.

From the intensive pharmacokinetic data, maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) during a dosing interval (AUC_{12} for twice daily administration; AUC_{24} for once daily administration), and time to C_{max} (T_{max}) were summarized. Intensive pharmacokinetic data analyses were performed by non-compartmental methods using Phoenix® WinNonlin® Version 6.0 (Pharsight, A Certara Company, St. Louis, MO).

Results

Patients

Seventy-five patients were screened and 38 were enrolled. The most common reasons for exclusion were abnormal laboratory analysis results (16 patients, 7 of whom had hemoglobin less than the lower limit of normal), positive urine drug screen for barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol (7 patients), and lack of verified