Clinical Infectious Diseases

BRIEF REPORT

Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir Combination Treatment in Patients With HIV/HCV Coinfection: Results of an Italian Compassionate Use Program

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Patients coinfected with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are at high risk of liver disease progression. We report a favorable safety profile and SVR12 rates of 96.7% among HIV/HCV coinfected patients participating in an Italian compassionate-use program of ombitasvir/paritaprevir/ritonavir + dasabuvir (OBV/PTV/r + DSV) ± ribavirin (RBV).

Keywords. HIV/HCV coinfection; DAA; IFN-free; antiviral therapy; anti-HCV therapy.

Worldwide, an estimated 5–10 million individuals with human immunodeficiency virus (HIV) are coinfected with hepatitis C virus (HCV) [1]. In Italy, approximately 30% of HIV-infected patients are coinfected with HCV, leading to an estimated 60 000 HIV/HCV coinfected individuals [2]. Coinfection negatively impacts the progression of HCV in several ways, including enhanced rates of HCV replication, decreased rates of HCV clearance, and increased fibrosis and hepatic decompensation [3]. Moreover, HIV-infected patients on antiretroviral therapy (ART) regimens with HCV-related liver disease have an increased risk of all-cause and liver-related mortality compared with HIV-negative individuals [4].

HCV virologic cure in HIV-coinfected patients reduces the risk of liver-related outcomes [5]. However, treatment with pegylated interferon (pegIFN) and ribavirin (RBV) yielded poor sustained virologic response (SVR) rates [5]. In Europe, there are several interferon (IFN)-free direct-acting antiviral (DAA) regimens approved for the treatment of HIV/HCV GT1 coinfected patients. In clinical studies, the all-oral, 3-DAA regimen of ombitasvir, paritaprevir, with the pharmacokinetic enhancer ritonavir, and dasabuvir (OBV/PTV/r + DSV) + RBV administered for 12 or 24 weeks has achieved SVR at week 12 post-treatment (SVR12) rates between 91% and 100% in HIV/HCV coinfected patients [6, 7]. With high rates of virologic response achieved with OBV/PTV/r + DSV + RBV in this patient population in clinical trials, it is increasingly important to evaluate this regimen in the real world.

Compassionate-use programs for DAAs give high-priority patients preapproval access to treatment and provide important data on safety and effectiveness in the real world. Here, we present data on the safety and effectiveness of OBV/PTV/r + DSV ± RBV in HIV/HCV GT1-infected patients who participated in a compassionate-use program coordinated by the Italian Society of Infectious and Tropical Diseases (SIMIT).

METHODS

Patients

The compassionate-use program provided access to treatment for patients with HCV GT1 or GT4 infection with or without compensated cirrhosis, including patients coinfected with HIV. The program enrolled 213 patients; 210 HCV GT1/HIV

Received 20 June 2016; editorial decision 16 November 2016; accepted 9 December 2016; published online February 9, 2017.

The results of this work were partially presented at the International Liver Congress, EASL, Barcelona, Spain,13–17 April 2016.

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Clinical Infectious Diseases® 2017;64(5):680–3

DOI: 10.1093/cid/ciw846

coinfected patients who completed 12 weeks of follow-up were evaluated in this analysis. All eligible patients were either treatment-naive or pegIFN/RBV-experienced, with or without cirrhosis, and were receiving a stable ART regimen (Supplementary Table 1).

Study Design

HCV GT1-infected patients were enrolled at 26 sites throughout Italy and received once-daily, coformulated OBV/PTV/r (25/150/100 mg) and twice-daily DSV (250 mg) plus RBV. Patients with cirrhosis received 24 weeks of treatment and those without received 12 weeks of treatment. HCV GT1b-infected patients without cirrhosis received OBV/PTV/r + DSV for 12 weeks, whereas those with cirrhosis received OBV/PTV/r + DSV + RBV for 24 weeks. RBV was administered twice-daily according to body weight and label recommendations [8]. Patients receiving a ritonavir-boosted ART regimen discontinued the ritonavir component of their ART regimen as recommended by the local OBV/PTV/r + DSV label [9, 10].

All patients in the study provided written informed consent, and the study was conducted in accordance with the International Conference on Harmonization guidelines, applicable regulations, and the principles of the Declaration of Helsinki. All authors had access to the study data and reviewed and provided feedback on all subsequent versions of the manuscript and made the decision to submit the manuscript for publication.

Study Assessments

Investigators performed laboratory testing, patient visits and follow-up according to the sites' local standards, whereas safety and effectiveness assessments were performed at the discretion of the investigators. Because this was a compassionate-use program in a real-world setting, missing laboratory assessments were permitted.

The primary endpoint for effectiveness was the percentage of patients achieving SVR12 (HCV RNA <25 IU/mL [lower limit of quantitation, LLOQ]). HCV RNA testing was performed by each site's local laboratory. Secondary analyses included the percentage of patients with on-treatment virologic failure (breakthrough, defined as a confirmed HCV RNA level ≥25 IU/mL after achieving HCV RNA <25 IU/mL) or post-treatment relapse (defined as a confirmed HCV RNA level ≥25 IU/mL during the post-treatment follow-up window in patients who had HCV RNA below the LLOQ at the end of treatment).

Data on AE severity and relation to study drugs were collected by physicians, reported in the databases, and communicated to investigators throughout the study.

Statistical Analysis

Analyses for effectiveness were performed in the intent-to-treat (ITT) population, defined as all enrolled patients that received at least 1 dose of study drug. Analyses were performed using Epi Info™, a public domain suite of interoperable software tools designed by the Centers for Disease Control and Prevention (CDC).

RESULTS

Patients

Two-hundred and thirteen HCV GT1-infected patients with HIV/HCV coinfection were enrolled. In total, 210 patients completed 12 weeks of follow-up and were included in the analysis (HCV RNA was undetectable at end of treatment in the 3 enrolled patients that were not included in the current analysis). The ITT population comprised 74.8% males and 98.6% white race; 11.0% had liver stiffness of >12.5 kPa (F4), 66.2% were infected with HCV GT1a. Complete baseline demographics are presented in Supplementary Table 1.

Effectiveness

HCV RNA suppression was rapid in HIV/HCV coinfected patients; 85.1% of patients with data available had HCV RNA levels below LLOQ at treatment week 4, by the end of treatment 98.6% of patients reached SVR. The overall SVR12 rate was 96.7% (203/210). Percentages of patients with HCV RNA levels below the LLOQ during treatment, at end of treatment, and post-treatment are presented in Figure 1. GT1 subtype, presence of cirrhosis, prior treatment history, baseline platelet count, CD4+ count, and HIV viral load had no impact on SVR12 rates. SVR12 rates were significantly higher ($P = .01$) among patients with baseline HCV RNA <1 000 000 IU/mL versus those with HCV RNA ≥1 000 000 IU/mL.

Seven patients did not achieve SVR12; 6 experienced virologic failure, and 1 prematurely discontinued treatment at week 6. Four GT1b-infected patients experienced virologic failure; 2 experienced virologic breakthrough between treatment weeks 8 and 12, and 2 relapsed between end of treatment and post-treatment week 12. Upon retesting, 1 patient who relapsed was found to be infected with HCV GT3a. Two GT1a-infected patients relapsed between end of treatment and post-treatment week 12. Disease and virologic characteristics of patients that experienced virologic failure are presented in Supplementary Table 2.

Impact of OBV/PTV/r + DSV ± RBV Treatment on Liver Function

Compared with baseline, mean AST, ALT, and hemoglobin were significantly lower at end of OBV/PTV/r + DSV ± RBV treatment ($P < .001$), whereas mean platelet count and total bilirubin were significantly higher ($P < .001$) (Supplementary Figure 1).

Maintenance of HIV-1 Suppression and Immunologic Response

Before enrollment, 121 patients (57.6%) modified their ART regimen. Compared with baseline, there were no significant ($P > .05$) changes at end of treatment in the proportion of patients with HIV RNA <50 copies/mL, mean CD4+ cell

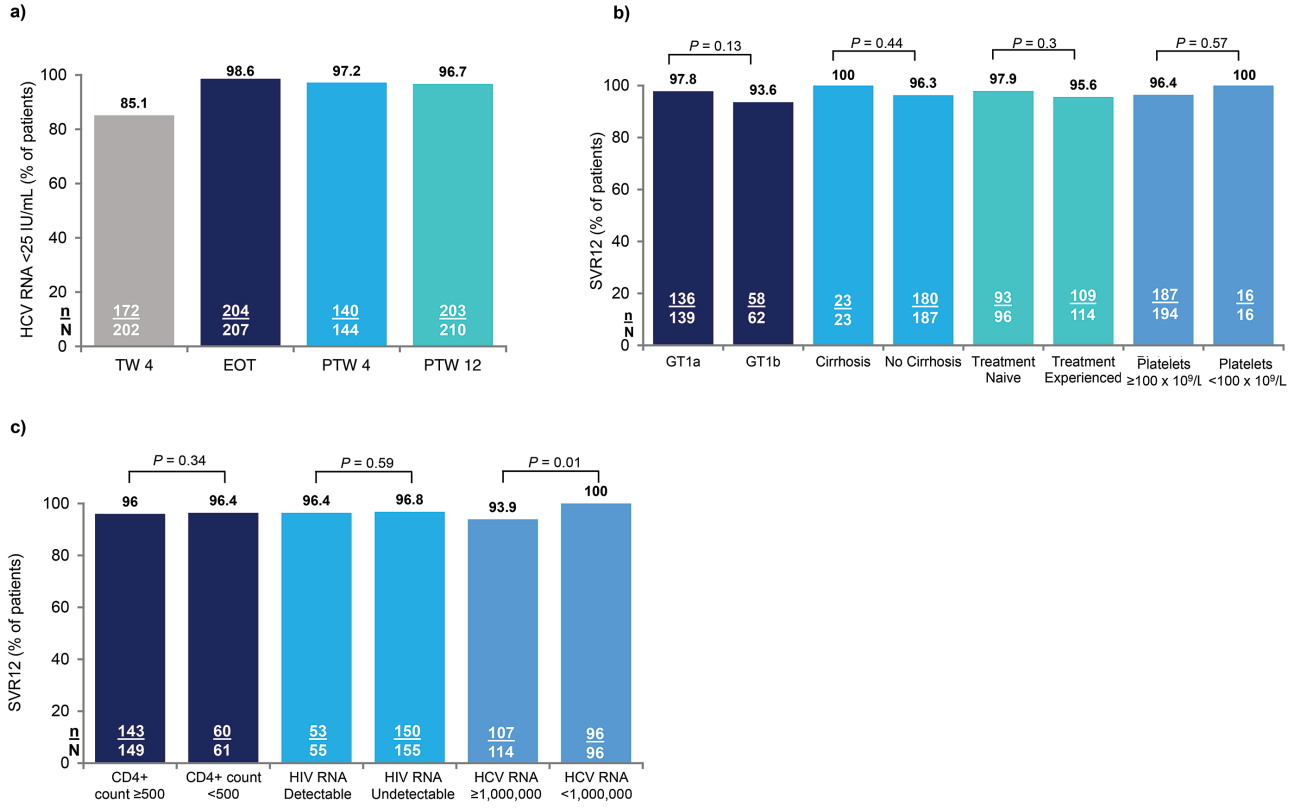

Figure 1. HCV RNA < 25 IU/mL during treatment with OBV/PTV/r + DSV ± RBV, at 4 weeks and end of treatment, and at post-treatment weeks 4 and 12. *A*, HCV RNA <25 IU/mL during treatment. *B*, SVR12 rates by baseline genotype, cirrhosis status, prior treatment history, and platelet count. *C*, SVR12 rates by CD4+ count, HIV viral load, and baseline HCV RNA. Abbreviations: DSV, dasabuvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OBV, ombitasvir; RBV, ribavirin; SVR, sustained virologic response.

counts, proportion of CD4+ cells, or CD4+ /CD8+ ratio (Supplementary Figure 2). Complete information on baseline ART regimen is presented in Supplementary Table 1.

Safety

Treatment-emergent AEs occurred in 88 (41.9%) patients. One (0.5%) patient experienced a serious AE (hospitalization due to a cardiac episode); which was not considered related to study drugs. This patient continued treatment and achieved an SVR12. No patient experienced an AE leading to discontinuation of study drugs, and no deaths were reported (Supplementary Table 3).

DISCUSSION

In this compassionate-use program, patients with HIV/HCV GT1 coinfection treated with OBV/PTV/r + DSV ± RBV for 12 or 24 weeks achieved an SVR12 rate of 96.7%, similar to SVR12 rates reported in clinical trials [6, 7]. Of the patient subgroups analyzed, only baseline HCV viral load had an impact on SVR12 rates. Markers of liver function, including ALT, AST, and platelet count, significantly improved at end of treatment compared with baseline, suggesting that treatment with OBV/PTV/r + DSV ± RBV is associated with normalization of liver function.

In this study, 57.6% of patients modified their ART regimen at start of OBV/PTV/r + DSV ± RBV treatment; however, change of ART treatment had no impact on the proportion of patients with undetectable HIV RNA or on CD4+ parameters at end of OBV/PTV/r + DSV ± RBV treatment.

OBV/PTV/r + DSV ± RBV was generally well tolerated, with no patient discontinuing treatment due to an AE. Compared with baseline, mean hemoglobin was significantly ($P < .001$) lower at end of treatment, whereas mean total bilirubin was significantly ($P < .001$) higher at end of treatment; however, these changes were not considered to be clinically relevant. Increases in bilirubin levels reported here are consistent with those described in previous safety analyses of OBV/PTV/r + DSV ± RBV [11]. Increases in bilirubin levels reported in previous analyses were self-resolving, predominately indirect, and related to the inhibition of the bilirubin transporters OATP1B1/1B3 by PTV and to RBV-induced hemolysis [18], not due to OBV/PTV/r + DSV hepatotoxicity.

In conclusion, our findings suggest that OBV/PTV/r + DSV ± RBV is safe and effective in compassionate-access programs for patients with HCV genotype 1 infection and HIV coinfection, a high-priority patient population.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors,

so questions or comments should be addressed to the corresponding author.

Notes

Authors' contributions. M.A. and SIMIT contributed to the conception and design of the study.

All the authors participated in revising the article critically for important intellectual content and gave approval of the final version to be submitted.

M.A. and L.S. contributed to critical revision of the article.

A.A., L.M., S.S., G.R., A.D.B., AS, R.B., V.B., A.D.L., A.C., H.H., G.T., A.D.A.M., C.M.M., G.D.P., S.B., M.P., A.S., A.G., N.B., B.C., A.G., G.P., V.V., A.C., A.P., C.P., and D.S. performed patients' enrollment, treatment, and data collection.

M.A., L.S., and E.T. contributed to collection, assembly, analysis, and interpretation of data.

Acknowledgments. This study was coordinated by the Italian Society of Infectious and Tropical Diseases (SIMIT). We are particularly grateful to Carlo Pasetto, Jelena Petrovic MD, Fabio Buelli MD, Valentina Gallinaro MD, and Simona Crosara for their support, and we are also grateful to AbbVie. Medical writing support was provided by Elizabeth Cottle of Medical Expressions.

Disclosures. M.A., A.A., G.R., A.D.L., H.H., A.D.A.M., G.D.P., M.P., and B.C. have received speaker fees, travel grants, and consulting fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, ViiV Healthcare, and Janssen-Cilag.

A.D.B. and R.B. have received speaker fees and consulting fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, ViiV Healthcare, Janssen-Cilag, and Roche.

A.C. has received consulting fees from Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and ViiV Healthcare.

C.M.M. has received speaker fees, travel grants, and consulting fees from Abbott/Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, ViiV Healthcare, Janssen-Cilag, Astellas, Novartis, and Pfizer.

A.G. has received speaker fees, travel grants, and consulting fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, ViiV Healthcare, Janssen-Cilag, Astellas, Boeringher, Novartis, Pfizer, and Roche.

V.V. has received speaker fees from Abbvie.

A.C. has received speaker fees, travel grants, and consulting fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme,ViiV Healthcare, Janssen-Cilag, and Basilda.

L.S. has received travel grants from Gilead Sciences and Merck Sharp & Dohme.

Funding. AbbVie provided study drugs at no charge which were distributed through a competitive enrollment program. No additional financial support was provided for this study.

Potential conflicts of interest. All authors: No potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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