Received: 16 October 2018 | Revised: 28 February 2019 | Accepted: 22 March 2019

DOI: 10.1111/jvh.13109

SHORT COMMUNICATION

JOURNAL OF VIRAL HEPATITIS JVH WILEY

Efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir with low-dose ribavirin in patients with chronic hepatitis C virus genotype 1a infection without cirrhosis

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Funding information
AbbVie sponsored the study (NCT02609659); contributed to its design; and participated in the collection, analysis, and interpretation of the data and in the writing, reviewing and approval of the publication.

Abstract

Patients infected with hepatitis C virus (HCV) treated with interferon-free direct-acting antivirals may still require ribavirin. However, ribavirin is associated with adverse events that can limit its use. This open-label, multicentre, Phase 3 study evaluated the safety and efficacy of ombitasvir/paritaprevir/ritonavir + dasabuvir (OBV/PTV/r + DSV) with low-dose ribavirin for 12 weeks in genotype 1a-infected patients without cirrhosis. The primary efficacy endpoint was sustained virologic response at post-treatment Week 12 (SVR12). The primary safety endpoint was haemoglobin <10 g/dL during treatment and decreased from baseline. Overall, 105 patients enrolled. The SVR12 rate was 89.5% (n/N = 94/105; 95% CI, 83.7-95.4). The study did not achieve noninferiority versus the historic SVR12 rate for OBV/PTV/r + DSV plus weight-based ribavirin. Five patients experienced virologic failure, four discontinued, and two had missing SVR12 data. Excluding nonvirologic failures, the SVR12 rate was 94.9% (n/N = 94/99). One patient met the primary safety endpoint. OBV/PTV/r + DSV plus low-dose ribavirin offers an alternative option for patients in whom

full-dose ribavirin may compromise tolerability, although noninferiority to the weight-based ribavirin regimen was not met.

KEYWORDS
genotype 1a, GEODE-II, hepatitis C virus, interferon-free therapy, low-dose ribavirin

1 | INTRODUCTION

Ribavirin remains a component of several direct-acting antiviral (DAA) regimens currently recommended for treating chronic hepatitis C virus (HCV) infection.[1] If indicated, ribavirin is administered daily in two divided doses based on body weight (1000 mg for <75 kg; 1200 mg for ≥75 kg), with appropriate dose reductions in patients with renal dysfunction.[2] However, ribavirin treatment can be associated with increased rates of adverse events (AEs), especially anaemia, which may necessitate ribavirin dose reductions or discontinuation that can potentially lower sustained virologic response at post-treatment Week 12 (SVR12).[3]

Treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir (OBV/PTV/r + DSV) with and without full-dose ribavirin for 12 weeks achieved SVR12 rates of 97% and 90%, respectively, in genotype (GT)1a-infected patients without cirrhosis.[4] The lower SVR12 rate in the ribavirin-free arm was attributed to a higher virologic failure rate versus full-dose ribavirin (7.8% vs 2.0%), mostly due to virologic relapse (5.2% vs 1.0%).[4] Although ribavirin-related AEs and laboratory abnormalities were more frequent with full-dose ribavirin, discontinuation rates were low with either regimen.

The GEODE-II study evaluated the safety and efficacy of OBV/PTV/r + DSV coadministered with low-dose ribavirin for 12 weeks in GT1a-infected patients without cirrhosis who were either HCV treatment-naïve or had prior interferon-based treatment experience.

2 | METHODS

GEODE-II (NCT02609659) was a Phase 3, open-label, multicentre study. Patients (≥18 years) infected with GT1a without cirrhosis were treated for 12 weeks with once-daily OBV/PTV/r (25 mg/150 mg/100 mg) plus twice-daily DSV (250 mg) coadministered with low-dose, once-daily ribavirin (600 mg). The study comprised of screening, 12-week treatment and 24-week follow-up periods. Patients who had prior experience with (pegylated) interferon with or without ribavirin were allowed to participate. Exclusion criteria included a history of drug or alcohol abuse within 6 months prior to the study drug administration that could preclude protocol adherence (see Supporting Information for full eligibility criteria).

The primary efficacy endpoint was the percentage of patients achieving SVR12. Secondary efficacy endpoints were on-treatment virologic failure and post-treatment relapse (see Supporting Information). For resistance testing, regions encoding NS3, NS5A or NS5B from available baseline samples, as well as post-baseline samples in patients experiencing virologic failure, were analysed. Variants that potentially confer resistance to DAAs were identified (see Supporting Information). Blood samples were collected at each visit, and plasma concentrations of study drugs were determined using validated assays.

The primary safety endpoint was the percentage of patients with plasma haemoglobin concentration <10 g/dL during treatment and decreased from baseline. AEs and laboratory abnormalities were evaluated. Ribavirin doses were reduced per prespecified protocol guidelines if haemoglobin decreases occurred. If efficacy treatment adjustment criteria were met (see Supporting Information), patients were switched to weight-based ribavirin.

Efficacy and safety analyses were performed on all patients who received ≥1 dose of study drug (intention-to-treat [ITT] population). SVR12 was also analysed in the modified ITT (mITT) population, which excluded nonvirologic failures. For SVR12 rates, two-sided 95% confidence intervals (CIs) were calculated using the normal approximation to the binomial distribution. Noninferiority of OBV/PTV/r + DSV plus low-dose ribavirin against the historical threshold[4] for OBV/PTV/r + DSV plus weight-based ribavirin was achieved if the 95% CI lower bound for SVR12 was >92%. SVR12 rates in the presence or absence of baseline polymorphisms were compared using Fisher's exact test.

The study protocol was approved by the independent ethics committee or institutional review board at each study centre and conducted in accordance with the Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

3 | RESULTS

A total of 105 patients enrolled from 10 sites in the United States; all received ≥1 study drug dose. Ninety-nine patients completed treatment and six discontinued treatment prematurely (primary reasons: AE, n = 1; loss to follow-up [LTFU], n = 1; noncompliance, n = 1; other, n = 3 [patient decision, incarceration, hospitalisation]). Ninety-seven patients completed the study and eight discontinued, six of whom were LTFU. No patients switched to full-dose ribavirin.

Most patients were white (85.7%), female (52.4%), HCV treatment-naïve (88.6%) and had minimal fibrosis (F0-F1, 81.0%). High percentages of patients reported a history of drug abuse or prior use of behavioural mood-modifying drugs (76.2%) or a history of alcoholism (81.0%) (Table S1).

By ITT analysis, 89.5% of patients achieved SVR12 (n/N = 94/105; 95% CI, 83.7-95.4). The lower bound 95% CI was <92%. One patient

TABLE 1 Treatment-emergent adverse events and post-baseline laboratory abnormalities

	N = 105
Adverse events, n (%)	
Any AE	77 (73.3)
Any severe AE	3 (2.9)
Any serious AE[a]	3 (2.9)
Any AE possibly related to DAAs	44 (41.9)
Any AE leading to study drug discontinuation[b]	2 (1.9)
Any AE leading to ribavirin dose modification[c]	2 (1.9)
Deaths	0
Common AEs (≥10%)	
Fatigue	29 (27.6)
Headache	14 (13.3)
Insomnia	12 (11.4)
Nausea	11 (10.5)
Laboratory abnormalities, n (%)[d]	
Haemoglobin	
Grade 2 (<10 to 8 g/dL)	1 (1.0)
Grade ≥3 (<8 g/dL)	0
Alanine aminotransferase	
Grade 2 (>3-5 × ULN)	1 (1.0)
Grade ≥3 (>5 × ULN)	1 (1.0)
Aspartate aminotransferase	
Grade 2 (>3-5 × ULN)	0
Grade ≥3 (>5 × ULN)	1 (1.0)
Total bilirubin	
Grade 2 (>1.5-3 × ULN)	5 (4.8)
Grade ≥3 (>3 × ULN)	0

Notes: Treatment-emergent AEs occurring from treatment initiation until 30 d post-treatment were coded using MedDRA version 19.0. Investigators determined AE severity and relatedness to drug treatment.

AEs, adverse events; DAAs, direct-acting antivirals; ULN, upper limit of normal.

[a]One case each of bipolar 1 disorder, psychotic disorder and cyclic vomiting syndrome. One serious AE had a reasonable possibility of being related to the study drug (bipolar 1 disorder).

[b]One patient with a history of bronchial asthma had nonserious AEs that had a reasonable possibility of being related to the study drug (chest pain, increased heart rate and dyspnoea), and one patient had a recurrent psychotic episode.

[c]Decreases in haemoglobin that led to ribavirin dose modification (adjusted to 400 mg daily).

[d]For laboratory abnormalities, N = 104.

had on-treatment virologic failure and four had post-treatment relapse. Six patients had nonvirologic failure (four discontinued treatment prematurely; two had missing SVR12 data). By mITT analysis, 94.9% achieved SVR12 (n/N = 94/99; 95% CI, 90.6-99.3). SVR12 rates for subgroups are provided in Table S2. One patient relapsed during the 24-week post-treatment period.

Overall, 73.3% of patients experienced ≥1 treatment-emergent AE (Table 1). Most AEs were mild or moderate in severity. Serious AEs were infrequent (2.9%; three events: bipolar 1 disorder, psychotic disorder, cyclic vomiting syndrome). The patient who experienced bipolar 1 disorder (possibly related to study drug) achieved SVR12. Two patients experienced AEs leading to premature treatment discontinuation.

One patient (1%) experienced haemoglobin <10 g/dL and decreased from baseline during treatment and required ribavirin dose interruption and modification to 400 mg; this patient experienced on-treatment virologic failure. Another patient experienced an AE of decreased haemoglobin leading to ribavirin dose modification; this patient achieved SVR12.

The respective prevalence of NS3-Q80K and OBV-specific baseline polymorphisms was 46.5% and 11.5% (Figure S1). The SVR12 rate (57.1%, 4/7) in patients with NS3-Q80K and OBV-specific polymorphisms in NS5A was lower than in patients without NS3-Q80K or OBV-specific polymorphisms (100%, 47/47; P = 0.001). SVR12 rates with OBV-specific baseline polymorphisms alone (100%, 4/4) or NS3-Q80K alone (94.7%, 36/38) were not different from the overall SVR12 rate (94.8%, 91/96), or the rate in patients without OBV-specific polymorphisms or NS3-Q80K (100%, 47/47). PTV- and DSV-specific baseline polymorphisms were rare (no impact on SVR12). Treatment-emergent substitutions were detected among the six virologic failures (Table S3).

Trough plasma concentrations of study drugs were generally comparable to C_{trough} values observed in similar studies where weight-based ribavirin was administered (AbbVie data on file), whereas low-dose ribavirin values were approximately 50% lower (Table S4).

4 | DISCUSSION

Low-dose, once-daily ribavirin may be administered to certain patients because of tolerability concerns.[1,5] A once-daily regimen may also improve treatment compliance.[6] In GEODE-II, we evaluated OBV/PTV/r + DSV plus low-dose 600-mg ribavirin for patients with GT1a infection. The SVR12 rate was 89.5% (ITT analysis), and noninferiority was not achieved versus OBV/PTV/r + DSV plus full-dose ribavirin.[4] The SVR12 rate was 94.9% by mITT analysis, demonstrating good efficacy in patients who completed 12-weeks treatment. Six patients failed to achieve SVR12 because of premature treatment discontinuation or missing SVR12 data. The high prevalence of patients with a history of psychosocial disorders may have accounted for the high rate of nonvirologic failures.

The presence of OBV-specific baseline polymorphisms in combination with NS3-Q80K was associated with low SVR12 rates (57.1%), suggesting a role for baseline resistance testing. However, the number of patients who had this combination was low (n = 7), limiting the interpretation of this finding.

The safety profile of this regimen was consistent with that observed in pivotal studies.[4,7,8] Ribavirin exposures were approximately 50% lower than in historical controls receiving full-dose ribavirin. This could explain the favourable improvements in ribavirin-related laboratory abnormalities and dose modifications versus other studies.[4]

Study limitations included that GT1a-infected patients with compensated cirrhosis or HIV coinfection were excluded. These patients require ribavirin and may benefit from a low-dose regimen. The 12-week treatment duration may not have been sufficient to maintain SVR12 rates versus historical controls. Other limitations include the open-label study design, lack of contemporaneous control group and high rate of nonvirologic failures.

OBV/PTV/r + DSV plus low-dose ribavirin was associated with high SVR12 rates and good tolerability in GT1a-infected patients without cirrhosis. However, this regimen confers no clinical benefit beyond the full-dose combination or currently recommended DAA regimens[1] and was not developed further.

ACKNOWLEDGEMENTS

Paritaprevir was identified by AbbVie and Enanta. The authors would like to express their gratitude to the patients who participated in this study and their families, as well as all the trial investigators and their research staff, and would like to thank Mareike Bereswill, employee of AbbVie, for statistical support. Presented in part at the 67th Annual Meeting of the American Association for the Study of Liver Diseases, November 11–15, 2016, Boston, Massachusetts. Editorial support was provided by Paul MacCallum, PhD, of Fishawack Communications Ltd.; funded by AbbVie.

CONFLICT OF INTEREST

F Poordad received grant/research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept Pharmaceuticals and Merck; is a consultant/advisor for AbbVie, Bristol-Myers Squibb, Gilead Sciences and Merck. S Sedghi had nothing to disclose. P Pockros is a speaker/consultant/advisor for Gilead, AbbVie, Janssen and Bristol-Myers Squibb; received research support from Gilead, AbbVie, Janssen, Bristol-Myers Squibb, Merck, Conatus and Roche Molecular. N Ravendhran reported conflicts of interest for AbbVie, Gilead, Merck, Salix, Bristol-Myers Squibb; received research support from Bristol-Myers Squibb, Gilead, Merck and Salix. R Reindollar is an investigator in clinical trials/speaker/advisory board member for AbbVie. M Lucey received grant/research support from AbbVie, Gilead and Salix. M Epstein is a consultant for IM HealthScience; speaker for Pfizer and Salix. L Bank is a speaker for AbbVie; received research support from AbbVie, Gilead and Merck. D Bernstein is a consultant for Merck; received grant/research support from Gilead, Pharmasset, Vertex and Bristol-Myers Squibb; speaker and teacher for Gilead. R Trinh, P Krishnan, AR Polepally, K Unnebrink and M Martinez are employees of AbbVie and may hold stock or stock options. D Nelson received grant/research support from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, Genentech, Merck, Bayer, Idenix, Vertex and Janssen.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Poordad F, Sedghi S, Pockros PJ, et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir with low-dose ribavirin in patients with chronic hepatitis C virus genotype 1a infection without cirrhosis. *J Viral Hepat*. 2019;26:1027–1030. https://doi.org/10.1111/jvh.13109