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Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir With or Without Ribavirin in HCV-Infected Patients Taking Concomitant Acid-Reducing Agents

Mitchell L. Shiffman, MD¹, Vinod Rustgi, MD², Michael Bennett, MD³, Xavier Forns, MD⁴, Tarik Asselah, MD⁵, Ramon Planas Vila, MD⁶, Li Liu, MD⁷, Marcos Pedrosa, MD⁷, Jonathan Moller, MD⁷ and Nancy Reau, MD⁸

OBJECTIVES: Acid-reducing agents (ARAs) and proton-pump inhibitors (PPIs) that increase gastric pH can alter the bioavailability of antiviral drugs, particularly relevant in patients with advanced liver disease caused by chronic hepatitis C virus (HCV) infection seeking therapy. Using integrated data from six phase 3 studies, we report the safety and efficacy of the 3-direct-acting antiviral (DAA) regimen containing ombitasvir (OBV, an NS5A inhibitor), ritonavir-boosted paritaprevir (PTV/r, an NS3/4A protease inhibitor), and dasabuvir (DSV, an NS5B polymerase inhibitor) with or without ribavirin (RBV) for HCV genotype 1 patients taking concomitant ARAs and PPIs.

METHODS: Treatment-naïve or peginterferon/RBV treatment-experienced patients with or without compensated cirrhosis received OBV/PTV/r and DSV with or without weight-based RBV. Rates of sustained virologic response (SVR), defined as HCV RNA below the lower limit of quantification, 12 weeks post-treatment (SVR12) and safety were evaluated in patients who were receiving concomitant ARAs.

RESULTS: Among 2,053 patients enrolled and dosed with study drug, 410 (20%) were receiving concomitant ARAs; of these, 308 (15%) were taking concomitant PPIs. Rates of SVR12 were 95.9% (95% confidence interval (CI) 93.5–97.4%) among patients receiving an ARA, and 96.3% (95% CI 95.3–97.2%) in patients not receiving a concomitant ARA. Similarly, among patients receiving a PPI or not, SVR12 was achieved in 95.1% (95% CI 92.1–97.0%) and 96.4% (95% CI 95.5–97.2%), respectively. Response rates were high regardless of treatment regimen (with or without RBV), and among patients receiving a standard or high dose of PPIs. Regarding safety, adverse events and serious adverse events were more frequently reported in patients taking concomitant ARAs, though baseline population differences may have played a role.

CONCLUSIONS: In phase 3 trials of OBV/PTV/r plus DSV and RBV in HCV genotype 1-infected patients, SVR12 rates were high regardless of ARA/PPI use or PPI dose. These data support the co-administration of this regimen with ARAs including PPIs.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/ajg>

Am J Gastroenterol 2016; 111:845–851; doi:10.1038/ajg.2016.108; published online 5 April 2016

INTRODUCTION

Acid-reducing agents (ARAs), particularly proton-pump inhibitors (PPIs), are the most commonly prescribed medications in

North America and Western Europe for the relief of gastroesophageal reflux disease, peptic ulcer disease, and gastric hyperacidity symptoms. Through terminal blocking of the gastric proton pump,

¹Liver Institute of Virginia, Bon Secours Health System, Newport News and Richmond, Virginia, USA; ²Thomas E. Starzl Transplantation Institute, Pittsburgh, Pennsylvania, USA; ³Medical Associates Research Group, San Diego, California, USA; ⁴Liver Unit, Hospital Clinic, CIBERehd, IDIBAPS, Barcelona, Spain; ⁵Centre de Recherche sur l'Inflammation, Inserm UMR 1149, Université Paris Diderot, AP-HP Hôpital Beaujon, Clichy, France; ⁶Hospital Germans Trias i Pujol, CIBERehd, Badalona, Spain; ⁷AbbVie Inc., North Chicago, Illinois, USA; ⁸Rush University Medical Center, Chicago, Illinois, USA. **Correspondence:** Mitchell L. Shiffman, MD, Liver Institute of Virginia, Bon Secours Health System, 5855 Bremono Road, Suite 509, Richmond, Virginia 23226, USA. E-mail: mitchell_shiffman@bshsi.org

Received 20 October 2015; accepted 23 February 2016

H⁺ ion secretion into the gastric lumen is irreversibly inhibited. Similarly, histamine H₂ antagonists prevent signaling of gastric acid production, thus, are often used to treat heartburn and dyspepsia. Elevated gastric pH can adversely affect concomitant oral medication bioavailability; therefore, careful examination of these interactions should be assessed when considering prescription of new drugs in patients taking ARAs.

Recent advances in the treatment of hepatitis C virus (HCV) infection have shown direct-acting antivirals (DAAs) to be highly effective for eradication of HCV in patients with various viral genotypes, both with and without cirrhosis. All DAAs for the treatment of HCV infection interact with drug metabolizing enzymes and/or drug transporters and should be assessed for dose adjustment requirements or contraindications with concomitant medications (1). In addition to the possibility of drug–drug interactions (DDIs) between ARAs and HCV DAAs, gastric pH can also effect DAA bioavailability due to increased or decreased pharmacokinetics (2–4). As a result, sub-therapeutic levels of antiviral drugs may lead to failure to achieve sustained virologic response (SVR). Omeprazole has been reported to reduce the area under the concentration-time curve (AUC) of ritonavir-boosted protease inhibitors by 75%; consequently, concomitant use of atazanavir, an HIV antiretroviral, and PPIs is considered contraindicated (2). The HCV NS5A inhibitor ledipasvir has reduced solubility as pH increases, thus, the prescribing information for ledipasvir/sofosbuvir cautions against concomitant use of antacids, H₂ antagonists, and PPIs, particularly doses of PPIs above the standard recommendation (4). Though clinical trial data do not exist for ledipasvir/sofosbuvir co-administered with ARAs or PPIs, real-world data have emerged, indicating that PPI usage at baseline was associated with a higher rate of virologic failure (5).

The HCV 3-DAA regimen of co-formulated ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and dasabuvir (DSV) with or without ribavirin (RBV) is approved for the treatment of chronic HCV genotype 1 infection in many countries including the United States, Japan, Canada, and countries in the European Union. Ritonavir and PTV are predominantly metabolized by CYP3A. Owing to inhibition of CYP3A activity, ritonavir boosting of protease inhibitors is common with antiretroviral agents and increases the AUC 5- to 80-fold, depending on the protease inhibitor boosted. The AUC of PTV is increased approximately 50-fold by ritonavir boosting, allowing for once-daily dosing (6). DSV is predominantly metabolized by CYP2C8 with minor metabolism by CYP3A, and OBV is metabolized by amide hydrolysis. Finally, OBV, PTV, and DSV all inhibit UGT1A (7). In 24 DDI studies conducted with 31 compounds to evaluate the effects of OBV, PTV, ritonavir, and DSV on concomitant medications, and vice versa, co-administration with omeprazole did not change plasma exposures of any drug (8).

Patients treated with OBV/PTV/r plus DSV with or without RBV achieved high rates of SVR 12 weeks post treatment (SVR12) in phase 3 trials (9–13). Unlike the phase 3 trials of other HCV DAA regimens (14–17), the six phase 3 trials of OBV/PTV/r plus DSV with or without RBV permitted concomitant use of ARAs, even at dosages higher than the prescribing information recommended dosage for each ARA or PPI (9–13). In this analysis, we

evaluated the integrated safety and efficacy from phase 3 trials of this 3-DAA regimen with or without RBV in patients with HCV genotype 1 infection who were receiving a concomitant ARA.

METHODS

Study populations and treatments

This *post hoc* analysis included the efficacy populations from patients enrolled in the six phase 3 trials, which included HCV treatment-naïve or peginterferon/RBV treatment-experienced patients without cirrhosis or with compensated cirrhosis. Sensitivity analyses were also conducted on the subset of patients who received the label-recommended regimen described in **Supplementary Table 1** online. SAPPHERE-I (9) and SAPPHERE-II (10) were randomized, double-blind, placebo-controlled trials in non-cirrhotic HCV genotype 1-infected patients with no prior HCV treatment history or treatment experienced with peginterferon/RBV, respectively. PEARL-II was an open-label, randomized trial comparing the 3-DAA regimen with RBV or placebo in place of RBV in peginterferon/RBV treatment-experienced non-cirrhotic patients with HCV genotype 1b infection (13). PEARL-III and PEARL-IV were double-blind randomized trials comparing the 3-DAA regimen with or without RBV in treatment-naïve patients without cirrhosis with genotype 1b and 1a infection, respectively (12). All patients in these five studies received 12 weeks of OBV/PTV/r 25 mg/150 mg/100 mg once-daily plus DSV 250 mg twice-daily with or without weight-based RBV. Finally, TURQUOISE-II (11) was an open-label randomized trial comparing 12 vs. 24 weeks of OBV/PTV/r plus DSV and RBV in HCV genotype 1-infected patients with compensated cirrhosis. Study eligibility criteria have been published previously (9–13).

Any medications received from the time of signing informed consent through HCV post-treatment day 30 were recorded. Allowed concomitant ARA use included antacids, H₂ blockers (cimetidine, famotidine, ranitidine), and PPIs (omeprazole, esomeprazole, dexlansoprazole, lansoprazole, pantoprazole, and rabeprazole). For the purposes of these analyses, the standard dosage of omeprazole, esomeprazole, and rabeprazole was considered ≤20 mg/day, ≤30 mg/day for dexlansoprazole, ≤15 mg/day for lansoprazole, and ≤40 mg/day for pantoprazole; dosages above these thresholds were considered a high dosage.

Efficacy and safety assessments

Virologic response was defined as a plasma HCV RNA below the lower limit of quantification (LLOQ=25 IU/ml) using the Roche COBAS TaqMan real-time reverse transcriptase-PCR assay version 2.0 (Roche Molecular Systems, Pleasanton, CA), and the primary efficacy assessment was SVR12. Efficacy and safety were assessed in all patients of the studies' efficacy populations, defined as all patients taking at least one dose of co-formulated OBV/PTV/r and DSV, and subgrouped by concomitant use (yes vs. no) of any ARA. In addition, subgroups defined by concomitant PPI use (yes vs. no) were also investigated. Rates of SVR12 were also evaluated in patients taking ARA dosages higher than the standard prescribing recommendations.

Safety was assessed in all patients who received at least one dose of study drug. Treatment-emergent adverse events were collected from time of study drug initiation until 30 days post treatment. Serious adverse events were collected until the end of each study.

Statistical analysis

SAS (SAS Institute) for the UNIX operating system was used for all analyses. Intra-regimen baseline categorical variables were compared between patients taking concomitant ARAs or not using a Chi-square test or Fisher's exact test; continuous variables

were compared using a Wilcoxon rank-sum test. 95% confidence intervals (CIs) were calculated using the Wilson score method. Response rates in those receiving concomitant ARAs were compared with those not receiving concomitant ARAs using the Fisher's exact test. Rates were also compared in those taking standard vs. high dosages of ARAs using the Fisher's exact test.

Multivariate logistic regression analysis was performed on the efficacy population to determine whether concomitant PPI use was associated with achievement of SVR12 or a predictor of virologic failure. Categorical variables included in the analysis were concom-

Table 1. Baseline demographics and disease characteristics of patients by concomitant ARA use while treated with OBV/PTV/r+DSV with or without RBV

Regimen	OBV/PTV/r+DSV+RBV		OBV/PTV/r+DSV	
	Yes (N=334)	No (N=1,214)	Yes (N=76)	No (N=429)
Concomitant ARA use				
Male	200 (59.9)	724 (59.6)	39 (51.3)	230 (53.6)
Age, mean years±s.d.	55.3±9.3***	51.0±10.9	54.5±10.5**	50.4±11.4
Black race	21 (6.3)	65 (5.4)	9 (12.0)	34 (7.9)
BMI, mean kg/m ² ±s.d.	28.0±4.3***	26.1±4.1	27.6±4.6*	26.4±4.2
HCV GT1a	202 (60.5)	654 (53.9)	46 (60.5)***	158 (36.8)
HCV RNA, mean log ₁₀ IU/ml±s.d.	6.5±0.6	6.5±0.6	6.5±0.7	6.4±0.7
IL28B non-CC	260 (77.8)	956 (78.7)	50 (65.8)**	341 (79.5)
<i>Geographic region</i>				
USA	179 (53.6)***	438 (36.1)	44 (57.9)	185 (43.1)
Europe	122 (36.5)	574 (47.3)	20 (26.3)	161 (37.5)
Rest of world	33 (9.9)	202 (16.6)	12 (15.8)	83 (19.3)
Concomitant PPI use	250 (74.9)	NA	58 (76.3)	NA
<i>Prior pegIFN/RBV treatment experience</i>				
Naïve	175 (52.4)***	768 (63.3)	67 (88.2)	347 (80.9)
Relapser	45 (13.5)	125 (10.3)	5 (6.6)	28 (6.5)
Partial response	39 (11.7)	82 (6.8)	1 (1.3)	25 (5.8)
Null response	75 (22.5)	239 (19.7)	3 (3.9)	29 (6.8)
<i>Fibrosis stage^a</i>				
F0–1	133 (39.8)***	707 (58.3)	37 (49.3)**	294 (68.7)
F2	44 (13.2)	152 (12.5)	19 (25.3)	82 (19.2)
F3	29 (8.7)	102 (8.4)	19 (25.3)	51 (11.9)
F4	128 (38.3)	252 (20.8)	0 (0)	1 (0.2)
History of diabetes	39 (11.7)***	76 (6.3)	8 (10.5)	20 (4.7)
History of gastroesophageal reflux disease	143 (42.8)***	48 (4.0)	40 (52.6)***	17 (4.0)
History of gastritis	28 (8.4)***	32 (2.6)	6 (7.9)*	8 (1.9)
History of peptic ulcer disease	16 (4.8)***	17 (1.4)	7 (9.2)**	7 (1.6)
History of dyspepsia	7 (2.1)*	8 (0.7)	3 (3.9)*	2 (0.5)

ARA, acid-reducing agent; BMI, body mass index; DSV, dasabuvir; HCV, hepatitis C virus; OBV, ombitasvir; pegIFN, pegylated interferon; PPI, proton-pump inhibitor; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; s.d., standard deviation.

Values are n (%), unless otherwise denoted.

*, **, and *** denote statistical significance at the $P < 0.05$, 0.01, and 0.001 levels comparing concomitant ARA use or not.

^aFibrosis stage missing for three patients.

itant PPI use, sex, race, HCV genotype 1 subtype (1b vs. non-1b), IL28B genotype (CC vs. non-CC), prior HCV treatment status, cirrhosis, treatment regimen (with vs. without RBV), geographic region (US vs. rest of world), geographic region (Europe vs. rest of world), history of diabetes, history of depression or bipolar disorder, history of bleeding disorders, and former injection drug use. Continuous variables were baseline age, body mass index (BMI), weight, HCV RNA, and alanine aminotransferase level.

RESULTS

Patients

Within the six phase 3 trials, 2,053 patients were enrolled comprising the efficacy population and received OBV/PTV/r plus DSV with or without RBV. Among all patients dosed, 20.0% (410/2053) were receiving a concomitant ARA including 21.6% (334/1548) of patients receiving OBV/PTV/r plus DSV with RBV and 15.0% (76/505) of patients receiving OBV/PTV/r plus DSV alone. Overall, 308 (15.0%) were taking at least one type of PPI during treatment; 156 omeprazole, 38 esomeprazole, 10 dexlansoprazole, 24 lansoprazole, 77 pantoprazole, and 9 rabeprazole. Baseline demographics for patients receiving the 3-DAA regimen with or without RBV and by concomitant ARA use are presented in **Table 1**. The baseline demographics and characteristics for subset of patients taking concomitant PPIs during HCV treatment are presented in **Supplementary Table 2**. Patients taking concomitant ARAs and PPIs were statistically older, had a higher BMI, and more frequently had compensated cirrhosis. Baseline statistically significant differences were also observed in the proportion of patients with prior treatment experience, enrolled at a study site within the United States, and medical histories of diabetes, gastroesophageal reflux disease, gastritis, peptic ulcer disease, and dyspepsia. Twenty-six percent of patients enrolled at sites within the United States were taking concomitant ARAs compared with 16% enrolled at European Union sites and 14% throughout the rest of the world.

Efficacy

Rates of SVR12 were high regardless of whether patients took concomitant ARAs during HCV treatment: 95.9% (393/410, 95% CI 93.5–97.4) among patients taking an ARA and 96.3% (1583/1643, 95% CI 95.3–97.2) among patients not taking an ARA (**Figure 1a**). Similarly, SVR12 rates were 95.1% (293/308, 95% CI 92.1–97.0) among patients receiving a PPI and 96.4% (1683/1745, 95% CI 95.5–97.2) among patients not taking concomitant PPIs. Response rates were also comparably high irrespective of whether patients were receiving a concomitant ARA/PPI by HCV treatment regimen (OBV/PTV/r plus DSV with RBV or without RBV), and among patients receiving a standard or high dose of PPIs (**Figure 1b**). Higher SVR12 rates were achieved in patients receiving a label-recommended regimen (**Supplementary Table 3**): 96.6% (199/206, 95% CI 93.2–98.3) in patients taking ARAs and 97.3% (855/879, 95% CI 96.0–98.2) not taking concomitant ARAs. The SVR12 rate in patients receiving a label-recommended regimen and taking concomitant PPIs was 95.9% (140/146, 95% CI 91.3–98.1)

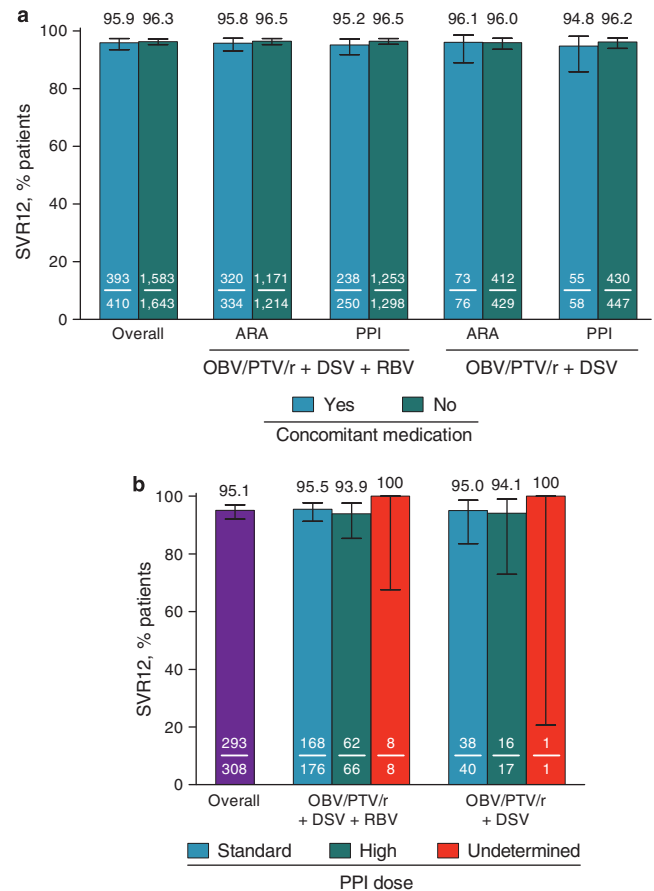


Figure 1. SVR12 rates in patients receiving OBV/PTV/r+DSV with or without RBV by concomitant use of ARAs or PPIs. SVR12 rates are shown by treatment regimen and concomitant use of ARAs or PPIs (**a**), and with standard, high, or undetermined PPI doses (**b**). The standard PPI dose for omeprazole, esomeprazole, and rabeprazole was ≤ 20 mg, ≤ 30 mg for dexlansoprazole, ≤ 15 mg for lansoprazole, and ≤ 40 mg for pantoprazole. Above these cutoffs was considered as a high PPI dose. ARA, acid-reducing agent; DSV, dasabuvir; OBV, ombitasvir; PPI, proton-pump inhibitor; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; SVR, sustained virologic response.

compared with 97.3% (914/939, 95% CI 96.1–98.2) in patients not taking PPIs. No statistically significant differences in SVR12 rates were found comparing patient subgroups based on whether ARAs were used concomitantly or not. Differences in SVR12 rates, overall and by individual PPIs with sufficient sample size for comparison, were not statistically different whether patients were taking standard vs. high dosages of PPIs. As might be expected, rates of relapse and on-treatment breakthrough were also comparable. Finally, multivariate logistic regression of factors predicting achievement of SVR12 did not identify concomitant PPI use as a predictor of lower SVR12 rates (odds ratio 0.95, 95% CI 0.52–1.80; $P=0.92$), nor virologic failure (odds ratio 1.30, 95% CI 0.64–2.67; $P=0.47$).

Safety

Although adverse events were more common overall in patients taking concomitant ARAs during HCV treatment, severe and

serious adverse events were increased only in the ARA-taking patients receiving OBV/PTV/r plus DSV and RBV (Table 2). No severe or serious adverse events were reported in patients taking concomitant ARAs not receiving RBV (i.e., genotype 1b-infected patients). Commonly occurring adverse events, including fatigue, nausea, diarrhea, and dyspepsia, were more frequent in patients taking concurrent ARAs. The frequencies of laboratory abnormalities were comparable regardless of concomitant ARA use. Premature study drug discontinuation rates were similar regardless of

ARA use; 1.0% in patients taking ARAs and 1.2% in patients not taking ARAs.

Differences in the safety profile of this 3-DAA regimen with or without RBV, particularly pertaining to frequency of anemia and hyperbilirubinemia, have been addressed previously (12,13). Serious adverse events observed in patients taking concomitant ARAs and OBV/PTV/r plus DSV with RBV did not have any evident commonality (Supplementary Table 4). Anemia, nausea, vomiting, and pneumonia were the only serious adverse events occurring

Table 2. Treatment-emergent adverse events and laboratory abnormalities in patients who did or did not receive concomitant ARAs, n (%)

Regimen	OBV/PTV/r+DSV+RBV		OBV/PTV/r+DSV	
	Yes (N=334)	No (N=1,214)	Yes (N=76)	No (N=429)
Any AE	323 (96.7)***	1,043 (85.9)	67 (88.2)**	313 (73.0)
Severe AE	24 (7.2)***	34 (2.8)	0	6 (1.4)
Serious AE	19 (5.7)***	26 (2.1)	0	7 (1.6)
AE leading to study drug discontinuation	6 (1.8)	10 (0.8)	0	2 (0.5)
AE leading to RBV dose modification	27 (8.1)	91 (7.5)	0	1 (0.2)
<i>AEs occurring in ≥10% in any subgroup</i>				
Fatigue	138 (41.3)**	391 (32.2)	29 (38.2)*	106 (24.7)
Headache	118 (35.3)*	354 (29.2)	24 (31.6)	104 (24.2)
Nausea	82 (24.6)*	226 (18.6)	11 (14.5)*	32 (7.5)
Diarrhea	63 (18.9)***	137 (11.3)	12 (15.8)	45 (10.5)
Pruritus	66 (19.8)*	173 (14.3)	7 (9.2)	24 (5.6)
Insomnia	58 (17.4)	164 (13.5)	7 (9.2)	19 (4.4)
Dyspepsia	47 (14.1)***	36 (3.0)	8 (10.5)**	9 (2.1)
Asthenia	43 (12.9)	150 (12.4)	4 (5.3)	16 (3.7)
Upper abdominal pain	37 (11.1)***	52 (4.3)	2 (2.6)	9 (2.1)
Dyspnea	34 (10.2)	91 (7.5)	3 (3.9)	7 (1.6)
Decreased appetite	30 (9.0)	73 (6.0)	8 (10.5)**	10 (2.3)
<i>Hemoglobin</i>				
Grade 2 (<10–8g/dl)	25 (7.5)	69 (5.7)	0	0
Grade 3 (<8–6.5g/dl)	2 (0.6)	4 (0.3)	0	0
Grade 4 (<6.5g/dl)	1 (0.3)	0	0	0
<i>Total bilirubin</i>				
Grade 2 (>1.5–3×ULN)	90 (27.0)**	247 (20.4)	4 (5.3)	25 (5.8)
Grade 3 (>3–20×ULN)	18 (5.4)	61 (5.0)	0	2 (0.5)
Grade 4 (>20×ULN)	0	1 (0.1)	0	0
<i>Alanine aminotransferase</i>				
Grade 3 (>5–20×ULN)	3 (0.9)	10 (0.8)	0	1 (0.2)
Grade 4 (>20×ULN)	1 (0.3)	4 (0.3)	0	0
<i>Aspartate aminotransferase</i>				
Grade 3 (>5–20×ULN)	0	6 (0.5)	0	1 (0.2)
Grade 4 (>20×ULN)	1 (0.3)	0	0	0

AE, adverse event; ARA, acid-reducing agent; DSV, dasabuvir; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; ULN, upper limit of normal.

*, **, and *** denote statistical significance at the $P < 0.05$, 0.01, and 0.001 levels comparing concomitant ARA use or not.

in more than one patient. Only 7 (1.7%) patients taking concomitant ARAs had serious adverse events assessed as having a reasonable possibility of being related to study drug or RBV. Serious adverse events assessed as being related to RBV included anemia, stroke, acute renal failure, chronic obstructive pulmonary disease, lactic acidosis, and cellulitis. Among the 19 patients experiencing serious adverse events taking ARAs with HCV treatment, 10 had compensated cirrhosis. Thus, the serious adverse event rate in patients taking ARAs was 7.8% (10/128) among patients with cirrhosis compared with 3.2% (9/281) in patients without cirrhosis receiving treatment with or without RBV.

DISCUSSION

Antiviral development has focused on balancing therapeutic drug levels without undesirable side effects, at the same time considering concomitant drug interactions. ARA use over-the-counter and by prescription is very common, particularly in individuals with gastroesophageal reflux disease, heartburn, or peptic ulcer disease. Orally administered medications, including new HCV DAAs, often rely on proper gastric or intestinal pH for optimal absorption. Despite the fact that omeprazole has been reported to reduce the AUC of ritonavir-boosted protease inhibitors, ARAs were not found to influence the drug exposures of the 3-DAA regimen of OBV/PTV/r plus DSV based on numerous DDI studies (8). Consistent with these observations, we report that this regimen with or without RBV achieved high SVR12 rates regardless of ARA/PPI use or PPI dosage in a large number of HCV genotype 1-infected patients, including those with cirrhosis who are prioritized for treatment.

Emergence of resistance-associated variants is a function of both drug potency and drug exposure. Suboptimal absorption of antiviral drugs may provide opportunities for drug-resistant quasiespecies or resistance-associated variants to emerge leading to HCV treatment failure. Concomitant administration of high PPI dosages and HCV DAAs that are sensitive to gastric pH may increase the risk for suboptimal drug exposures and the development of resistance-associated variants. Although initial HCV treatments with peginterferon and RBV alone did not have drug resistance concerns, their effectiveness and safety profiles left much to be desired. Drug resistance concerns have become more evident with the development of HCV DAAs that specifically interact with different non-structural proteins during viral replication. From our analysis, we observed high SVR12 rates in patients with pre-existing conditions necessitating higher than standard PPI dosages in whom pausing PPI therapy to facilitate HCV treatment may not be feasible. Among the common targets for HCV DAAs (i.e., NS3, NS5A, and NS5B), NS5A resistance-associated variants have been identified as being particularly persistent (18,19), and are associated with reduced SVR rates when present at baseline or upon retreatment.(20,21) Reports have shown that 94–96% of NS5A resistance-associated variants persist up to 96 weeks after relapse (18,19), thus, reducing the risk of developing resistance should be a priority until sufficient retreatment options are available. Accordingly, an HCV treatment option that permits concomitant use of higher PPI dosages is desirable for patients requiring higher-than-standard PPI doses.

Ledipasvir, an NS5A inhibitor, has reduced solubility as gastric pH increases that can lead to decreased drug exposure (4). Although concomitant use of ARAs was specifically excluded within phase 2 and 3 studies of ledipasvir/sofosbuvir, the label for ledipasvir/sofosbuvir recommends separating antacid administration by at least 4h, H2 antagonists by 12h, and omeprazole or equivalent PPI doses no higher than 20mg. Patients taking ARAs and PPIs were also excluded from phase 2 and 3 studies of the HCV regimen containing the NS3/4A protease inhibitor grazoprevir and NS5A inhibitor elbasvir (16,22). Approval of grazoprevir/elbasvir is expected in early 2016; thus, the label recommendations for concomitant ARA use remain unknown. Because ARAs were excluded from phase 3 registrational trials for these two HCV regimens, real-world data will be needed to elucidate ARA co-administration safety and effectiveness. A logistic regression analysis from the HCV TARGET registry, which included data from over 1,000 patients receiving ledipasvir/sofosbuvir regimens, identified PPI use at baseline as a negative predictor for SVR (5). Rates of SVR12 were 98.3% in patients without PPI use at baseline compared with 92.7% in patients taking PPIs at baseline (5). In contrast, concomitant PPI use with OBV/PTV/r plus DSV with or without RBV was not found to be a predictor of lower SVR12 rates or virologic failure by logistic regression.

In patients treated with OBV/PTV/r plus DSV with RBV, SVR12 rates were similar irrespective of whether concomitant ARAs including standard and high-dose PPIs were taken or not. This observation was despite the fact that, on average, patients taking ARAs were older, had a higher BMI, and more often had genotype 1a infection and cirrhosis. These baseline population differences may have played a role in the increased rates of adverse events recorded in patients taking concomitant ARAs, particularly the difference in proportion of patients with cirrhosis in whom advanced liver disease is associated with higher rates of adverse events (11,23). In addition, a higher proportion of patients receiving concomitant ARAs were enrolled at sites within the United States where reporting of adverse events has been observed to be higher among American populations in studies with the 3-DAA regimen (12). Not surprisingly, some events (e.g., dyspepsia, nausea, and diarrhea) were reported more often in individuals taking ARAs at baseline who had a higher prevalence of baseline gastric hyperacidity (i.e., gastroesophageal reflux disease, gastritis, peptic ulcer disease, and dyspepsia). The majority of serious adverse events were assessed to have no reasonable possibility of being related to study drug or RBV. Overall, the rate of treatment discontinuation due to adverse events was low and laboratory abnormalities were similar regardless of concomitant ARA use.

In conclusion, the findings of this *post hoc* analysis provide reassurance that the co-administration of OBV/PTV/r plus DSV with ARAs and PPIs does not negatively affect the chance for viral eradication. High SVR rates were achieved despite advanced fibrosis and concomitant ARA or PPI use.

ACKNOWLEDGMENTS

Medical writing support was provided by Douglas E. Dylla, PhD, of AbbVie.

CONFLICT OF INTEREST

Guarantor of the article: Mitchell L. Shiffman, MD.

Specific author contributions: Study investigators and took part in conducting the studies, collecting and interpreting the data: Mitchell L. Shiffman, Vinod Rustgi, Michael Bennett, Xavier Forns, Tarik Asselah, Ramon Planas Vila, and Nancy Reau. All authors provided critical revision during the drafting of the manuscript. All authors approved the final version of the manuscript submitted.

Financial support: AbbVie sponsored the studies, contributed to their designs, participated in the collection, analysis, and interpretation of the data, and in the writing, reviewing, and approval of the manuscript.

Potential competing interests: Mitchell L. Shiffman: Advisor: AbbVie, Achillion, Bristol-Myers Squibb, Gilead, Merck; grant/research support: AbbVie, Achillion, Beckman-Colter, Bristol-Myers Squibb, Gilead, Intercept, Lumena, Novartis; Speaker: AbbVie, Bayer, Gilead, Janssen, Merck. Vinod Rustgi: Research support: AbbVie, Gilead, Hyperion, Inovio; Advisory Board: AbbVie, Bristol-Myers Squibb, Gilead, Merck. Michael Bennett: Stock: AbbVie. Xavier Forns: Grant support: Janssen; Advisor: Janssen, Gilead, AbbVie. Tarik Asselah: Clinical investigator, speaker, and/or consultant for AbbVie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche. Ramon Planas Vila: Research support from Roche, MSD, BMS, Gilead, Janssen; advisory board/speaker for AbbVie, Roche, MSD, BMS, Gilead, Janssen; speaker for Roche, MSD, BMS, Gilead, Janssen. Li Liu, Marcos Pedrosa, Jonathan Moller: AbbVie employees and may hold AbbVie stock or options. Nancy Reau: Research support: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Merck; Consultant: AbbVie, Bristol-Myers Squibb, Gilead, Merck.

Study Highlights**WHAT IS CURRENT KNOWLEDGE**

- ✓ New 3-direct-acting antivirals (DAAs) against hepatitis C virus (HCV) genotype 1 have very high response rates.
- ✓ Drug exposures of some HCV DAAs are affected by gastric pH.
- ✓ The efficacy and safety of acid-reducing agent (ARA) and proton-pump inhibitor (PPI) concomitant use with DAAs needs further investigation.
- ✓ Bioavailability of ombitasvir (OBV), paritaprevir (PTV), ritonavir (r), dasabuvir (DSV), and ribavirin (RBV) is not influenced by omeprazole.

WHAT IS NEW HERE

- ✓ Response rates were comparably high in HCV patients receiving OBV/PTV/r+DSV±RBV and concomitant ARAs or PPIs.
- ✓ Treatment was well tolerated with few treatment discontinuations.

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