Concomitant Proton Pump Inhibitor Use Does Not Reduce the Efficacy of Elbasvir/Grazoprevir: A Pooled Analysis of 1,322 Patients With Hepatitis C Infection

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Concomitant proton pump inhibitor (PPI) use reduces plasma concentrations of certain nonstructural protein 5A inhibitors, which are key components of modern hepatitis C infection (HCV) treatments. These reduced concentrations may decrease efficacy, leading to challenging treatment failures due to the development of resistance-associated substitutions. This post-hoc analysis assessed 12-week sustained viral response (SVR12) and pharmacokinetics of fixed-dose combination elbasvir/grazoprevir (EBR/GZR) in patients with HCV infection and self-reported PPI use. Data were derived from six phase 3 EBR/GZR trials with treatment-naive or treatment-experienced genotype 1- or 4-infected patients, with or without compensated cirrhosis. Baseline PPI use was defined as ≥7 consecutive days of use between study days −7 and 7. Bivariate analyses assessed PPI use and factors associated with SVR12 with sex, age (continuous and dichotomous), cirrhosis status, prior treatment status, baseline HCV RNA (continuous and dichotomous), HCV genotype, and baseline resistance-associated substitutions as variables in the models. Overall, 12% (162/1,322) of EBR/GZR-treated patients reported baseline PPI use. Of those, 96% achieved SVR12. In patients without PPI use, 97% achieved SVR12. PPI use was not a predictive factor in achieving SVR12 based on a univariate analysis ($P = 0.188$). In the bivariate models, none of the interaction terms involving PPI use were statistically significant. There was no significant effect of PPI usage, regardless of adjustment for considered factors. The estimated area under the curve and maximum concentration values for EBR were comparable among patients with and without reported PPI use. *Conclusion:* These results demonstrate that PPI use with EBR/GZR had no clinically significant effect on SVR12 rates in genotype 1/4-infected patients with or without compensated cirrhosis. (clinicaltrials.gov identifiers: NCT02092350, NCT02105467, NCT02105662, NCT02105688, NCT02105701, NCT02358044) (*Hepatology Communications* 2017;1:757-764)

Introduction

Use of proton pump inhibitors (PPIs) is commonplace. In the U.S. population, PPI use was noted in 7% of patients seen in emergency departments to 27% in nursing home environments.[1,2] In the United Kingdom, it is estimated that 15% of their population uses PPIs.[3] In addition, up to one third of hepatitis C virus (HCV)-infected patients use acid-reducing agents or PPIs[4] to relieve gastroesophageal reflux disease, erosive esophagitis, and gastric or duodenal ulcers. PPI use results in significant long-lasting elevation of intragastric pH through irreversible blocking of the gastric proton pump, and this may affect the absorption of concurrently administered medications that exhibit pH-dependent solubility.[5,6] Direct-acting antiviral agents (DAAs) have been the focus of recent advances in HCV infection treatment regimens, demonstrating remarkable efficacy and improved tolerability over

Abbreviations: AUC_{0-24}, area under the curve within 24 hours; CI, confidence interval; C_{max}, maximum concentration; DAA, direct-acting antiviral agent; EBR, elbasvir; GM, geometric mean; GT, genotype; GZR, grazoprevir; HCV, hepatitis C infection; mFAS, modified full analysis set; NS5A, nonstructural protein 5A; PK, pharmacokinetics; PPI, proton pump inhibitor; SVR12, 12-week sustained viral response.

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previous treatment regimens across viral genotypes.[7] However, it has been noted that increased gastric pH can meaningfully decrease the bioavailability of some DAAs, including ledipasvir and velpatasvir, which are both HCV nonstructural protein 5A (NS5A) inhibitors.[8,9] Therefore, the prescribing information for ledipasvir/sofosbuvir and for sofosbuvir/velpatasvir caution against co-administration of PPIs and other acid-reducing agents.[8,9] Importantly, the decreased bioavailability with some DAAs is not a metabolic/transporter drug–drug interaction with PPIs but rather is a result of changes in gastric pH that may also occur in the elderly as a normal part of the aging process.[10] This decreased bioavailability can lead to treatment failure, resulting in resistance-associated substitutions that may be challenging to treat, especially because salvage therapy may contain acid-sensitive therapy.

Grazoprevir (GZR), a potent once-daily NS3/4A protease inhibitor, and elbasvir (EBR) a potent once-daily NS5A protein inhibitor, are components of an EBR/GZR fixed-dose combination therapy indicated for the treatment of chronic HCV genotype (GT) 1 or 4 infection.[12-14] EBR/GZR treatment has demonstrated consistently high sustained viral response (SVR) rates in patients with HCV GT1 and GT4 infection, including treatment-naive[15] and treatment-experienced patients,[16-18] patients with stage 4/5 chronic kidney disease,[19] patients co-infected with HIV,[20] and patients who inject drugs.[21]

GZR is an acidic compound; therefore, an increase in gastric pH is not expected to reduce its bioavailability. EBR is a basic compound, and increasing gastric pH decreases its solubility. However, EBR is prepared using an enabled formulation, which is not a simple coating of the tablet but rather reduces the negative pH effect on its bioavailability. Phase I study results demonstrated no clinically meaningful effect of PPI use on the pharmacokinetics (PK) of the fixed-dose combination of EBR/GZR in healthy volunteers.[22] The current report presents a pooled analysis of studies in the phase 3 clinical program of EBR/GZR that assessed the 12-week SVR (SVR12) in patients with HCV with self-reported PPI use. In addition, the PK of EBR/GZR in a subset of these patients is also assessed.

Patients and Methods

This was a post-hoc analysis of data derived from the six phase 3 EBR/GZR trials that included treatment-naive or treatment-experienced GT1- or GT4-infected patients, with or without compensated cirrhosis. The analysis incorporated data from only those phase 3 trials in which the marketed fixed-dose combination tablet of EBR/GZR, which included the enabled formulation of EBR, was used. C-SURFER (Merck protocol PN052 [deferred arm only], NCT02092350) was a phase 3, randomized, blinded, placebo-controlled study of the safety and efficacy of EBR/GZR in patients with HCV GT1 infection and chronic kidney disease (stage 4-5 with or without hemodialysis dependence).[19] C-EDGE-TN (Merck

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protocol 060, NCT02105467) was a global, randomized, blinded, placebo-controlled study of the efficacy and safety of EBR/GZR conducted in treatment-naive adults with GT1, 4, or 6 infection, with or without cirrhosis.[15] C-EDGE CO-INFECTION (Merck protocol PN061, NCT02105662) was an uncontrolled, nonrandomized, phase 3, open-label, single-arm global study of the efficacy and safety of EBR/GZR in treatment-naive adults with chronic HCV GT1, 4, or 6 and HIV co-infection, with or without cirrhosis.[20] C-EDGE CO-STAR (Merck protocol PN062, NCT02105688) was a randomized, placebo-controlled, double-blind, global trial of the efficacy and safety of EBR/GZR in treatment-naive patients with chronic HCV GT 1, 4, or 6 infection who injected drugs and who were at least 80% adherent to visits for opioid agonist therapy.[21] C-EDGE-TE (Merck protocol PN068, NCT02105701) was a phase 3, randomized, parallel-group, open-label study of the efficacy and safety of EBR/GZR in HCV GT1-, 4-, or 6-infected patients who had failed prior treatment with peginterferon/ribavirin.[18] C-EDGE Head-to-Head (Merck protocol PN077 [EZR/GZR arm], NCT02358044) was a phase 3, randomized, open-label, active comparator trial in GT1- or 4-infected patients to assess safety and tolerability of EBR/GZR versus sofosbuvir plus peginterferon/ribavirin.[23] All studies were conducted in accordance with the principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies. Patients provided written informed consent before any study procedures.

Patients with HCV GT1 or 4 with baseline viral load >10,000 IU/mL, who were either treatment-naive or had prior treatment failures and either with or without cirrhosis, were included in this analysis. In each study, patients received EBR/GZR once daily, without regard to food intake, as either a fixed-dose combination of EBR 50 mg/GZR 100 mg for 12 weeks or a fixed-dose combination of EBR 50 mg/GZR 100 mg + ribavirin for 16 weeks. Use of PPIs and other acid-reducing agents was allowed. The objective was to compare SVR12 after the end of all study therapy (defined as HCV RNA <15 IU/mL) in patients with and without consistent baseline PPI use. In addition, characteristics associated with achievement of SVR12 were assessed in conjunction with PPI use.

Analyses were done in the modified full analysis set (mFAS) population, which excludes administrative discontinuations. Self-reported baseline PPI use was defined as ≥7 consecutive days of use between day −7 and day 7. Baseline characteristics were summarized. A series of bivariate logistic regression models was performed on the mFAS population to determine which factors were associated with achievement of SVR12 and to ascertain whether consistent PPI use had any affect. Consistent PPI use was included in every bivariate model; other variables included in the analyses were sex, age (continuous and dichotomous [<64 years and ≥65 years]), cirrhosis status, prior treatment status, baseline HCV RNA (continuous and dichotomous [≤800,000 IU/mL and >800,000 IU/mL]), HCV genotype (1a, 1b, or 4), and presence of baseline resistance-associated substitutions (NS5A resistance-associated substitutions at amino acid positions 28, 30, 31, or 93). An additional set of multivariate logistic regression models was also considered using forward selection, backward selection, and stepwise selection procedures. All multivariate models included consistent PPI use, and a two-sided $\alpha = 0.10$ was used for inclusion and exclusion of the other variables from these models.

Population PK data were available for analysis from five of the six studies (Merck protocols PN052 [deferred arm only], PN060 [immediate arm only], PN061, PN062, and PN068). The EBR area under the plasma concentration time curve (AUC) and maximum concentration (C_{max}) for individual patients were estimated based on the EBR concentrations of sparsely collected PK samples using a population PK modeling approach. The population PK model EBR was developed based on pooled PK data from patients in phase 1 to phase 3 studies. The model was evaluated using simulation-based visual predictive checks and showed that the model accurately characterized the central tendency of the observed data and that an appropriate distribution of the observed data fell within the 5th and 95th percentiles of model-simulated data. These results indicate that the models adequately describe the EBR concentration data from the clinical studies.

All statistical analyses were conducted using SAS 9.3.

Results

A total of 1,322 patients were included in the mFAS population analysis. In the overall mFAS population, the majority of patients were white (72.5%), male (65.2%), without cirrhosis (78.5%), and with a mean (±SD) age of 51.1 (±10.8) years. Most patients were treatment naive (80.7%), and 68.4% had a

TABLE 1. BASELINE CHARACTERISTICS IN THE MODIFIED FULL ANALYSIS SET POPULATION

	Consistent Baseline PPI Use n = 162	No Consistent Baseline PPI Use n = 1,160	All Patients n = 1,322
Sex, n (%)			
Male	104 (64.2)	758 (65.3)	862 (65.2)
Female	58 (35.8)	402 (34.7)	460 (34.8)
Age, mean (SD)	55.9 (8.4)	50.4 (10.9)	51.1 (10.8)
BMI, kg/m^2, mean (range)	27.7 (15.8, 47.8)	26.2 (11.0, 52.8)	26.3 (11.0, 52.8)
Race, n (%)			
White	108 (66.7)	850 (73.3)	958 (72.5)
Black	44 (27.2)	191 (16.5)	235 (17.8)
Asian	4 (2.5)	94 (8.1)	98 (7.4)
Other	6 (3.7)	25 (2.2)	31 (2.3)
Cirrhosis status, n (%)			
Yes	47 (29.0)	237 (20.4)	284 (21.5)
No	115 (71.0)	923 (79.6)	1,038 (78.5)
Prior treatment status, n (%)			
Treatment experienced	43 (26.5)	212 (18.3)	255 (19.3)
Treatment naive	119 (73.5)	948 (81.7)	1,067 (80.7)
Baseline HCV RNA			
≤800,000 IU/mL	39 (24.1)	379 (32.7)	418 (31.6)
>800,000 IU/mL	123 (75.9)	781 (67.3)	904 (68.4)
HCV Genotype, n (%)			
1a	105 (64.8)	643 (55.4)	748 (56.6)
1b	50 (30.9)	431 (37.2)	481 (36.4)
4	7 (4.3)	86 (7.4)	93 (7.0)
Presence of baseline RASs	17 (10.5)	158 (13.7)*	175 (13.3)*

*Presence of any substitution in NS5A amino acid positions 28, 30, 31, or 93 at baseline. Five patients did not have baseline NS5A sequencing performed and are thus excluded from the denominators for No Consistent Baseline PPI Use and All Patients for this term.
Abbreviations: BMI, body mass index; RAS, resistance-associated substitution.

baseline viral load of >800,000 IU/mL (Table 1). Overall, 12% (162/1,322) of EBR/GZR-treated patients reported baseline use of PPIs. PPI users were slightly older (mean age 56 years compared with 50 years for nonusers), more likely to be Black/African-American (27% versus 17% for nonusers), more likely to have cirrhosis (29% versus 20% for nonusers), and more likely to be treatment experienced (26% versus 18% for nonusers; Table 1).

A high proportion of patients achieved SVR12 regardless of consistent PPI use at baseline. In patients who reported consistent baseline use of PPIs, 155/162 (96%) achieved SVR12. In patients without consistent PPI use, 1,129/1,160 (97%) achieved SVR12 (Table 2). Consistent PPI use was not a predictive factor in achieving SVR12 based on univariate analysis (P = 0.188). In the bivariate models, none of the interaction terms involving PPI use was statistically significant, indicating that any potential effects of consistent PPI were similar across the factors considered. In addition, consistent PPI usage was not a statistically significant effect, regardless of adjustment for the factors considered (Table 2; Fig. 1). Results from the multivariate models were similar. All three variable selection procedures converged on the same final model, which included consistent PPI use (P = 0.555), age (P = 0.066), HCV GT (P = 0.001), and presence of baseline resistance-associated substitutions (P = <0.001).

Based on population PK modeling, the estimated AUC within 24 hours ($AUC_{0–24}$) and C_{max} values for EBR were comparable among patients with and without reported consistent PPI use (Fig. 2 and Table 3). The geometric mean (GM) AUC_{0-24} in patients taking EBR with consistent baseline PPI use was 2.42 μM•hour (95% confidence interval [CI], 2.26, 2.59), and in patients without consistent baseline PPI use, GM AUC_{0-24} was 2.28 μM•hour (95% CI, 2.22, 2.35; Table 3). Individual distribution of AUC_{0-24} or SVR12 was similar regardless of consistent PPI use at baseline, showing no correlation between consistent PPI use, EBR AUC_{0-24}, and SVR12 rate (Fig. 1A). The GM C_{max} in patients taking EBR with and without consistent baseline PPI use was 0.17 μM (95% CI, 0.16, 0.18) and 0.150 μM (95% CI, 0.15, 0.15),

TABLE 2. SVR12 RATES BY KEY BASELINE DEMOGRAPHIC FACTORS

Model Category	Demographic/ Baseline Parameter	Consistent Baseline PPI Use Observed SVR12 Rate (95% CI)	No Consistent Baseline PPI Use Observed SVR12 Rate (95% CI)
Overall	-	95.7% (155/162) (91.3, 98.2)	97.3% (1,129/1,160) (96.2, 98.2)
Sex	Female	96.6% (56/58) (88.1, 99.6)	98.5% (396/402) (96.8, 99.5
	Male	95.2% (99/104) (89.1, 98.4)	96.7% (733/758) (95.2, 97.9)
Age	<64 years	95.7% (133/139) (90.8, 98.4)	97.4% (1,047/1,075) (96.3, 98.3)
	≥65 years	95.7% (22/23) (78.1, 99.9)	96.5% (82/85) (90.0, 99.3)
Cirrhosis status	Cirrhotic	93.6% (44/47) (82.5, 98.7)	97.9% (232/237) (95.1, 99.3)
	Noncirrhotic	96.5% (111/115) (91.3, 99.0)	97.2% (897/923) (95.9, 98.2)
Prior treatment status	Treatment experienced	95.3% (41/43) (84.2, 99.4)	98.1% (208/212) (95.2, 99.5)
	Treatment naive	95.8% (114/119) (90.5, 98.6)	97.2% (921/948) (95.9, 98.1)
Baseline HCV RNA category	≤800,000	100% (39/39) (91.0, 100.0)	98.7% (374/379) (96.9, 99.6)
(≤800,000 vs >800,000)	>800,000	94.3% (116/123) (88.6, 97.7)	96.7% (755/781) (95.2, 97.8)
HCV genotype	GT 1a	94.3% (99/105) (88.0, 97.9)	96.0% (617/643) (94.1, 97.3)
	GT 1b	100% (50/50) (92.9, 100.0)	99.1% (427/431) (97.6, 99.7)
	GT 4	85.7% (6/7) (42.1, 99.6)	98.8% (85/86) (93.7, 100.0)
Presence of baseline RASs*	BL RASs present	82.4% (14/17) (56.6, 96.2)	88.6% (140/158) (82.6, 93.1)
	No BL RASs present	97.2% (141/145) (93.1, 99.2)	98.7% (984/997) (97.8, 99.3)

*Presence of any substitution in NS5A amino acid positions 28, 30, 31, or 93 at baseline. Five patients did not have baseline NS5A sequencing performed and are thus excluded from this summary; all 5 patients were classified as having no consistent baseline PPI use.
Abbreviations: BL, baseline; RAS, resistance-associated substitution.

respectively. Individual distribution of C_{max} or SVR12 was similar regardless of consistent PPI use at baseline, showing no correlation between consistent PPI use, EBR C_{max}, and SVR12 rate (Fig. 1B).

Discussion

The results of this pooled analysis of 1,322 patients showed that PPIs taken concomitantly for at least 7

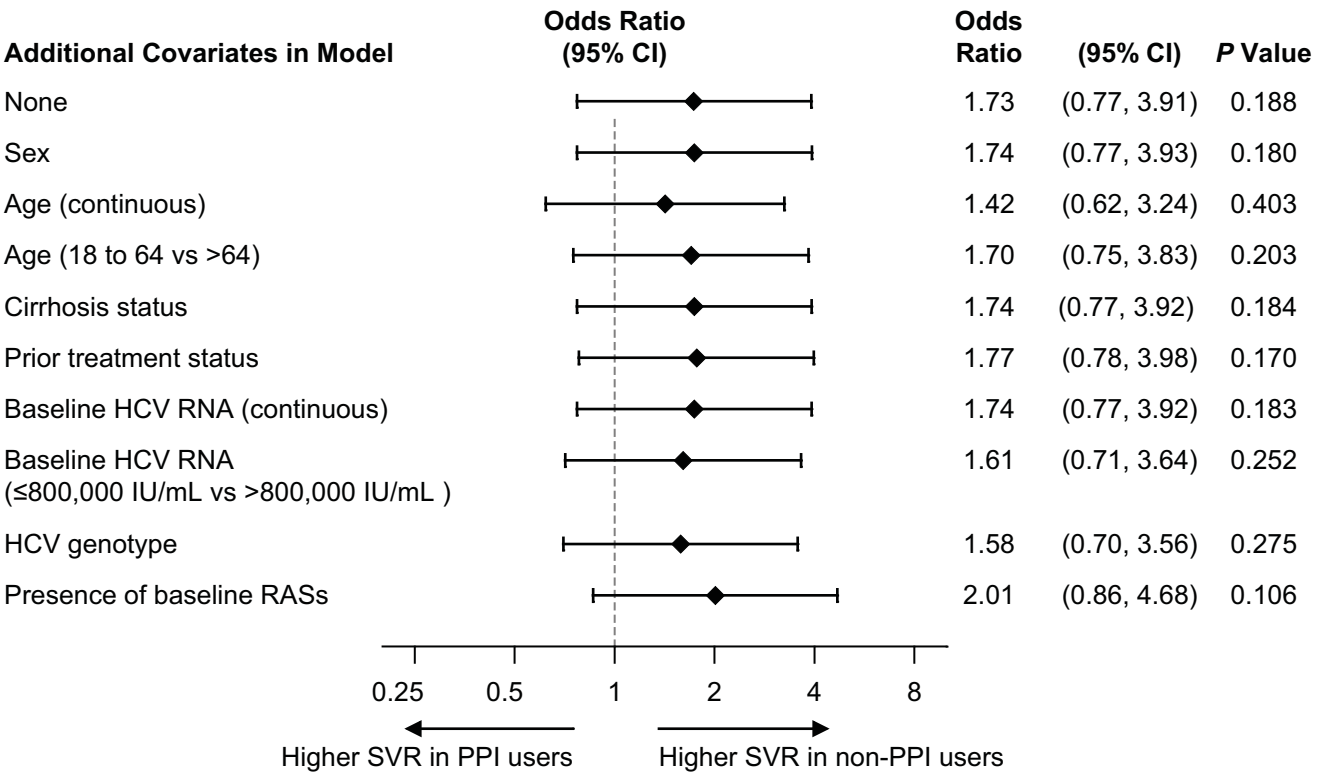

FIG. 1. Forest plot of bivariate regression models. Abbreviation: RAS, resistance-associated substitution.

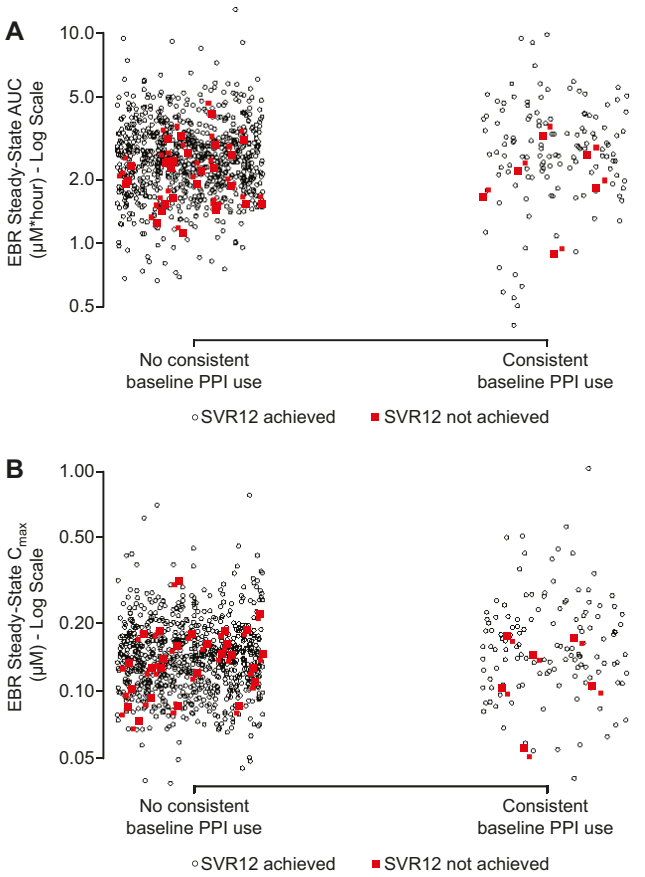

FIG. 2. Population PK modeling showing the estimated $AUC_{0\text{-}24}$ and C_{max} values for EBR. (A) Distribution of EBR AUC by SVR12 status and PPI use with at least 7 consecutive days of PPI use within days −7 to 7. (B) Distribution of EBR C_{max} by SVR12 status and PPI use with at least 7 consecutive days of PPI use within days −7 to 7.

consecutive days were not associated with reduced SVR12 rates with EBR/GZR treatment in patients with HCV infection. When included in logistic regression analyses, consistent PPI use was not a predictive factor in SVR12 achievement, even after adjusting for effects known to be associated with SVR12 or for which there was an imbalance between consistent PPI users and nonconsistent PPI users. The population PK results further support these findings, demonstrating no correlation between consistent PPI use, EBR $AUC_{0\text{-}24}$, and SVR12 rate.

This pooled analysis reported 12% of patients with consistent baseline PPI use, which is considerably lower than the 2014 estimate of 30% PPI use in HCV patients.[4] However, the proportion of patients falls within the range of overall estimated PPI use in the United States (7%-27%) and United Kingdom (15%),

TABLE 3. GEOMETRIC MEAN $AUC_{0\text{-}24}$ AND C_{MAX} IN PATIENTS TAKING EBR WITH AND WITHOUT CONSISTENT BASELINE PPI USE

	No Consistent Baseline PPI Use		Consistent Baseline PPI Use	
PK Parameter (EBR)	n	Value (95% CI)	n	Value (95% CI)
GM $AUC_{0\text{-}24}$ (μM•hour)	869	2.28 (2.22, 2.35)	136	2.42 (2.26, 2.59)
GM C_{max} (μM)	869	0.15 (0.15, 0.15)	136	0.17 (0.16, 0.18)

and it is in line with the overall number of patients (15%) reported in the Shiffman et al.[24] study assessing PPI use concomitantly with ombitasvir/paritaprevir/ritonavir plus dasabuvir. In contrast, it is substantially lower than that of the TARGET study, which assessed PPI use and SVR12 with ledipasvir/sofosbuvir treatment and reported 28% of patients using PPIs.[25] This difference could be due to differences in how PPI use was defined in each of the studies (TARGET has not published their definition), with the definition in the current analysis potentially restricting the number of patients included.

This is the first report of a pooled analysis assessing concomitant PPI use with EBR/GZR in a large population of patients with HCV infection. In the current analysis, the SVR12 rates observed in patients treated with EBR/GZR both with and without concomitant PPI use were high and comparable to previous results in patients treated with EBR/GZR.[15,19,20] Moreover, consistent baseline use of PPIs does not change the relationship between SVR12 and the other factors considered, including cirrhosis status, baseline viral load, HCV genotype, or presence of baseline resistance-associated substitutions. These results are in contrast to a study done in GT1-infected patients treated with ledipasvir/sofosbuvir in which PPI use was associated with a higher rate of virologic failure; the SVR12 rate was 98% without PPI use versus 93% with PPI use.[25] In contrast, the results of the current analysis were comparable with results of a recent study assessing SVR12 rates in patients treated with the four-drug combination of ombitasvir- paritaprevir-ritonavir and dasabuvir with and without concomitant acid-reducing agent use.[24] In that study, SVR12 rates were 96% (95% CI, 94%-97%) in patients with concomitant acid-reducing agent use and 96% (95% CI, 95%-97%) in patients without concomitant acid-reducing agent use. However, the population included in that study was limited to treatment-naive or peginterferon/ribavirin treatment-experienced patients with or without

compensated cirrhosis,[24] while the current analysis included patients who were treatment naive or experienced, with or without compensated cirrhosis, with chronic kidney disease, were HIV co-infected, had failed prior treatment with peginterferon/ribavirin, and were patients who injected drugs, demonstrating generalizable efficacy and clinical relevance across several populations of HCV patient types.

The bioavailability of some NS5A inhibitors has been shown to be particularly sensitive to changes in gastric pH. For example, the solubility of ledipasvir and velpatasvir decreases with increases in stomach pH, leading to decreased absorption and potentially decreased efficacy and reduced SVR rates, which was realized in the aforementioned TARGET study.[8,9,25] Based on the evidence, the prescribing information for ledipasvir/sofosbuvir and sofosbuvir/velpatasvir includes recommendations for separating administration of acid-reducing agents by at least 4 hours, H2 agonists by 12 hours, and dosing omeprazole and other comparable PPIs no higher than 20 mg.[8,9] Although no effect was observed on AUC_{0-24} in PK studies, standard doses of the PPI omeprazole or the H2-blocker famotidine decreased the C_{max} of ledipasvir by 4%-11%, and 17%-20%, respectively.[26] Conversely, the solubility of ombitasvir-paritaprevir-ritonavir and dasabuvir was not affected by concomitant use of omeprazole 40 mg; however, the C_{max} and AUC_{0-24} of omeprazole were both reduced (0.62 [90% CI, 0.48, 0.80] and 0.62 [90% CI, 0.51, 0.75], respectively),[27] potentially impacting the efficacy of the PPI.

EBR was formulated to reduce the effects of increasing gastric pH on its bioavailability; therefore, it is not surprising that the comparison of population PK data in the current analysis was consistent with the phase 1 study data, which demonstrated no meaningful changes in the PK of both EBR and GZR administered as the EBR/GZR fixed-dose combination in healthy volunteers with PPI use.[22] The current analyses in patients with HCV further demonstrates that concomitant use of PPIs does not impact the efficacy of EBR/GZR, indicating that the results are generalizable to a large population of patients with HCV GT1 or GT4 infection regardless of cirrhosis status, baseline viral load, HCV genotype, or presence of baseline resistance-associated substitutions. Taken together, the results of the current analysis along with the phase 1 study results indicate that EBR/GZR fixed-dose combination can be co-administered concomitantly without restrictions with PPIs and other acid-reducing agents with no impact on SVR12. Moreover, the enabled formulation of EBR is not a simple coating to prevent dissolution in the stomach; therefore, whether the tablet is administered intact or crushed is not expected to affect the reduced sensitivity of the enabled EBR formulation to pH changes.

In conclusion, there is no clinically significant effect of concomitant PPI use with EBR/GZR on SVR12 rates in HCV patients with or without cirrhosis infected with GT1 or GT4. Furthermore, PPI use was not associated with changes in SVR12 rates in patients with HCV infection based on age, cirrhotic state, HCV genotype, baseline viral load, or the presence of baseline resistance-associated substitutions.

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