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Gastric-acid-mediated drug–drug interactions with direct-acting antiviral medications for hepatitis C virus infection: clinical relevance and mitigation strategies

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Drug–drug interactions (DDIs) between direct-acting antiviral (DAA) medications and acid-reducing agents mediated by gastric acid represent an important issue in drug development and treatment, which could lead to impaired bioavailability and subtherapeutic plasma concentrations of DAA drugs and subsequently compromised treatment outcomes. However, identification of clinically relevant drug interactions associated with elevated gastric pH is not well characterized. Here, we present the first comprehensive analysis of the gastric-acid-mediated drug interactions with all novel DAA medications by analyzing and revisiting *in vitro* data, prospective DDI trials and retrospective assessments based upon Phase II and III studies, aiming toward an in-depth understanding of the clinical implications and mitigation strategies to circumvent such interactions.

Introduction

It has been documented that 20–30% patients with hepatitis C virus (HCV) infection receiving direct-acting antiviral (DAA) drugs require concurrent acid-suppression therapy for comorbidities, such as gastroesophageal reflux disease and other gastrointestinal disorders [1–3]. The use of acid-reducing agents (also known as acid-suppressive agents) is more common and frequent among those with HCV-related cirrhosis [2]. Acid-reducing agents, such as proton-pump inhibitors (PPIs) and histamine H2 antagonists, can alter the gastric environment for drug dissolution *in vivo* and absorption [4–6], thereby raising an important issue on drug–drug interactions (DDIs) between acid-reducing agents and DAA medications in the indicated patients. Considering the high prevalence of the acid-reducing agent usage among patients with HCV infection, it is crucial to figure out when and to what degree concurrent use with acid-reducing agents could result in clinically meaningful decreases in the bioavailability and overall exposure of DAA medicines and associated loss of clinical benefit of antiviral treatment.

In this review, we provide a comprehensive analysis of gastric-acid-mediated drug interactions with all novel DAA medications by analyzing and revisiting data derived from *in vitro*, prospective DDI trials, and retrospective assessments based upon Phase II and III studies from the literature and publicly accessible regulatory documents by the FDA [7] and the European Medicines Agency (EMA) [8]. To our knowledge, this is the first comprehensive review of such drug interactions with DAA medications, aiming toward a better understanding of the clinical implications and management of collaborative drug therapy. An in-depth understanding of gastric-acid-related DDI liability of DAA drugs can guide the development and establishment of mitigation strategies to minimize the extent of such DDIs to a clinically irrelevant level.

Gastric-acid-mediated drug–drug interactions with DAA medicines: clinical implications

Daclatasvir

Daclatasvir is a weak-base, DAA drug with a solubility decreasing from 20 mg/ml at pH 2 to 0.11 mg/ml and 0.015 mg/ml at pH 5 and 7, respectively (Table 1) [9,10]. Moreover, the therapeutic dose strength of daclatasvir at 60 mg cannot be expected to completely dissolve in 250 ml (i.e., the well-established volume for drug dissolution *in vivo*) of aqueous buffers over the pH range of 5–7 reached after pretreatment with acid-reducing agents. On the basis

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TABLE 1

Solubility information and gastric-acid-mediated drug interaction potential indicated by *in vitro* solubility data [7,8]

Compound	pKa	Solubility	pH-dependent solubility	Is solubility at pH 4.5–5.0 less than dose/250 ml?	Is solubility at pH 6.0–6.5 less than dose/250 ml?	Potential of gastric-acid-related DDIs based on *in vitro* data[a]
Daclatasvir	5.6 and 4.9	The solubility of daclatasvir is 0.11 mg/ml at pH 5, with strongly enhanced aqueous solubility at lower pH values	Yes	Yes	NA	Positive
Sofosbuvir	9.3	Solubility is generally pH-independent over the physiological pH range, 1.3 mg/ml at pH 1.2 (HCl), 2.0 mg/ml at pH 2 (HCl), 2.1 mg/ml at pH 4.5 (acetate buffer), 1.9 mg/ml at pH 6.8 (phosphate buffer) and 2.2 mg/ml at pH 7.7 (unbuffered) Biorelevant solubility is 1.8 mg/ml at FeSSIF (pH 5.0) and 2.1 at FaSSIF (pH 6.5)	Inconclusive	No	No	Negative
Ledipasvir	4.0 and 5.0	Ledipasvir is slightly soluble (1.1 mg/ml) below pH 2.3 and practically insoluble (<0.1 mg/ml) from pH 3 to pH 7.5	Yes	Yes	Yes	Positive
Velpatasvir	3.2 and 4.6	The solubility of velpatasvir decreases as pH increases, with an aqueous solubility <0.1 mg/ml above pH 5, 3.6 mg/ml at pH 2 and >36 mg/ml at pH 1.2. Biorelevant solubility is 0.1 mg/ml in FeSSIF (pH 5.0) and <0.1 mg/ml in FaSSIF (pH 6.5)	Yes	Yes	Yes	Positive
Voxilaprevir	−0.84[b] and 3.74[b]	Solubility is low (<0.1 mg/ml) and pH-independent, with a solubility of 0.2 mg/ml in either FaSSIF or FeSSIF	No	Yes	Yes	Negative
Elbasvir	4.81 and 5.88	Elbasvir is practically insoluble in water (<0.1 mg/ml) Solubility is 0.05 mg/l at pH 5, 0.008 mg/l at pH 7 and 0.02 mg/l at pH 9	Yes	Yes	Yes	Positive
Grazoprevir	<2.0 and 4.68	Grazoprevir is practically insoluble in water (<0.1 mg/ml) Solubility is 0.07 mg/l at pH 5, 13.6 mg/l at pH 7 and 85.9 mg/l at pH 9	Yes	Yes	Yes	Negative (owing to its acidic properties)
Simeprevir	2.85 and 5.24	Simeprevir is practically insoluble (<0.1 mg/ml) in aqueous media over the physiological pH range	No	Yes	Yes	Negative
Ombitasvir	2.5	Ombitasvir is practically insoluble (<0.1 mg/ml) in aqueous media at pH 1 (HCl) and pH 6.8 (phosphate buffer)	No	Yes	Yes	Negative
Paritaprevir	4.6	Paritaprevir is practically insoluble (<0.1 mg/ml) in aqueous media at pH 1 (HCl) and pH 6.8 (phosphate buffer)	No	Yes	Yes	Negative
Ritonavir	1.8 and 2.6	Aqueous solubility is 0.4 mg/ml at pH 1 and 1 μg/ml at pH 6.8	Yes	Yes	Yes	Positive
Dasabuvir	8.2 and 9.2	Dasabuvir is slightly soluble in water	NA	Yes	Yes	NA
Glecaprevir	4.0 and 11.7	It shows pH-dependent aqueous solubility, being practically insoluble at pH <5.1 and very slightly soluble at and above pH 6.6	Yes	Yes	No	Negative
Pibrentasvir	3.5, 4.1 and 11.6	It shows pH-dependent aqueous solubility, being very slightly soluble at pH 1.1 and practically insoluble at pH ≥2.1	Yes	Yes	Yes	Positive

Abbreviation: NA, not available.

[a] Based on the conceptual framework proposed by Zhang *et al.* [11], three criteria were used for predicting potential of gastric-acid-related DDIs: criterion 1 (weak base), criterion 2 (pH-dependent solubility, i.e., solubility at pH 6.0–6.5 < solubility at pH 1–2) and criterion 3 (solubility at pH 6.0–6.5 is <dose/250 ml). Only when all of the three criteria were adequately met was a drug judged as 'positive'. Notably, if drug solubility at pH 6.0–6.5 is inconclusive, the solubility value at pH 4.5–5.0 was served as a supplement in criterion 3. A volume of 250 ml denotes the typical quantity of water concomitantly taken by individual subjects during drug intake.

[b] Predicted pKa values from Drugbank database (https://www.drugbank.ca/).

of the FDA-proposed preliminary framework [11], acid-reducing agents, such as PPIs, H2-antagonists and antacids, could have a marked impact on daclatasvir bioavailability and total exposure.

It was shown that a low-fat meal did not significantly affect peak plasma concentration (C_{max}) and bioavailability of daclatasvir (Table 2) [9,10]. Whereas a high-fat meal decreased daclatasvir C_{max} and area under the plasma concentration–time curve extrapolated to infinity (AUC_{inf}) by 28% and 23%, respectively, compared with fasted conditions (Table 2) [9,10]. Considering the potency and safety profile of daclatasvir demonstrated in Phase III trials regardless of food intake [12], it is advised to take daclatasvir irrespective of food.

To assess the impact of concurrent acid-suppression therapy on daclatasvir absorption and exposure, a single dose of 60 mg daclatasvir was administered in the fasted state and 2 h after a single oral dose of 40 mg famotidine (Table 3) [9,10]. Famotidine reduced daclatasvir C_{max} by 44% without altering systemic daclatasvir exposure (within the bioequivalence limits of 80–125%). In another study for investigating gastric-acid-related DDIs between omeprazole and daclatasvir, pretreatment with omeprazole (40 mg once daily for six consecutive days) was conducted to achieve maximum acid suppression. Omeprazole reduced daclatasvir C_{max} slightly by 20%, whereas AUC_{inf} of daclatasvir was unaffected following concomitant use of omeprazole with 20 mg daclatasvir. By increasing daclatasvir dose to 60 mg, a 36% reduction in peak daclatasvir exposure was identified, whereas only <20% decrease in systemic daclatasvir exposure was observed in the presence of a steady-state level of omeprazole (Table 3). The diminished peak exposure of daclatasvir is unlikely to have any clinical meaningfulness, indicating that daclatasvir is well tolerated with PPIs or other acid-reducing agents.

Of note, in a population pharmacokinetic analysis involving 2149 patients receiving daclatasvir treatment in Phase II and III trials that included 18.5% (398 of 2149) patients taking the drug concurrently with acid-reducing agents, use of acid-reducing agents was not identified as a significant covariate on either oral clearance or absorption [13], showing a minor impact of gastric-acid modifiers on daclatasvir pharmacokinetics. Although no specific information pertaining to the type of acid-reducing agent, the timing of drug administration with reference to acid-reducing agents and the treatment frequency was available in the study, the findings from this population approach are generally consistent with dedicated DDI studies, supporting concurrent use of daclatasvir with acid-reducing agents if necessary.

Sofosbuvir-based regimens

Sofosbuvir

Sofosbuvir is a novel DAA medication indicated for the treatment of HCV infection as a component of a combination antiviral therapy regimen. The solubility of sofosbuvir is generally not dependent on pH, with an aqueous solubility of ~2 mg/ml across a wide ranging pH 2.0–7.7 (Table 1) [14,15]. Furthermore, the recommended dose of 400 mg appeared to be soluble in 250 ml or less of aqueous media at either pH 4.5–5.0 or pH 6.0–6.5 (Table 1). Despite the paucity of a dedicated trial for assessing gastric-acid-mediated DDIs for sofosbuvir as a single agent, the risk of such DDIs is expected to be low on the basis of *in vitro* solubility data judged along with the preliminary framework by the FDA [11]. As such, acid-reducing agents should not be contraindicated for use with sofosbuvir in patients with HCV infection.

In the presence of a high-fat meal, systemic sofosbuvir exposure was increased by >60%, whereas the systemic exposure of its predominant circulating metabolite GS-331007 was not changed (Table 2) [14,15]. The impact of a high-fat meal on sofosbuvir exposure was not considered to be clinically meaningful because of a very rapid conversion of sofosbuvir to its active metabolite GS-331007. Moreover, sofosbuvir was instructed to be given without regard to meals in Phase III trials for demonstrating the effectiveness of the drug as well as its safety [12,16]. Collectively, from a DDI perspective, concurrent use of sofosbuvir with acid-reducing agents in the absence or presence of a meal is warranted.

Ledipasvir/sofosbuvir

Ledipasvir/sofosbuvir is a fixed-dose, sofosbuvir-based DAA combination of 90 mg ledipasvir and 400 mg sofosbuvir. The solubility of ledipasvir decreases with elevated pH (Table 1) [17,18], indicating gastric-pH-related DDI susceptibility for ledipasvir/sofosbuvir. Food-effect studies suggested that ledipasvir/sofosbuvir can be administered with or without a meal, because systemic exposure of either ledipasvir or the predominant circulating metabolite of sofosbuvir, GS-331007, was not altered when administered under fed conditions (Table 2) [17,18]. Dedicated DDI studies were performed under fasted and fed conditions to eliminate confounding factors introduced by food intake [17]. As presented in Table 3, a 40–50% decrease in peak and systemic ledipasvir exposure was observed when ledipasvir was administered as a single agent with a meal and 2 h after the last dose of 20 mg omeprazole once daily for 6 days. However, peak and systemic exposure of ledipasvir, sofosbuvir and GS-331007 were affected only slightly by <15% when administered as ledipasvir/sofosbuvir under fasted conditions simultaneously with omeprazole (20 mg). Additional prospective trials for pH-related DDIs with famotidine were conducted in the fed state to explore the impact of meal intake on such interactions further. Unlike the previous observations that omeprazole modestly impaired the fed bioavailability of ledipasvir, systemic exposure of ledipasvir, sofosbuvir and GS-331007 were changed only slightly (<25%) when it was given as ledipasvir/sofosbuvir under fed conditions either simultaneously with or 12 h apart from famotidine 40 mg (Table 3). Collectively, it is advised to take ledipasvir/sofosbuvir under fasted conditions at the same time as omeprazole 20 mg or other PPIs (equivalent to omeprazole 20 mg) once daily whenever necessary, although ledipasvir/sofosbuvir can be administered irrespective of meal intake. Alternatively, ledipasvir/sofosbuvir can be given with famotidine or other H2 antagonists irrespective of food.

Importantly, a retrospective analysis of clinical data from 2099 participants in an observational study showed that use of PPI was associated with a twofold lower odds ratio for achieving sustained virologic response (SVR) relative to no use of PPI [3]. Another assessment using data from a real-world cohort of 1979 patients with HCV infection receiving ledipasvir/sofosbuvir treatment also revealed that twice-daily use of PPI appeared to lead to a lower odds ratio of SVR 12 weeks post completion of treatment (SVR12) for patients with liver cirrhosis [2]. These analyses indicated overdosing of PPI could result in a declined virologic response, supporting the avoidance of the use of PPI at a dose higher than

TABLE 2

Effect of meals on the pharmacokinetics of direct-acting antivirals [7–10,14–22,24–25,27–30,38–40]

DAA medication	Meal type	N	Changes in pharmacokinetics[a]	Meal intake in Phase III trials	Recommendations
Daclatasvir	High-fat (951 kcal, 492 kcal from fat)	23	AUC_{inf} ↓23%, C_{max} ↓28%	Daclatasvir was administered irrespective of meals in Phase III trials	Daclatasvir can be administered irrespective of meal intake
	Low-fat (277 kcal, 41 kcal from fat)	23	AUC_{inf} ↔, C_{max} ↔		
Sofosbuvir	High-fat	39	Sofosbuvir: AUC_{inf} ↑80%, C_{max}↓16%; GS-331007: AUC_{inf} ↔, C_{max} ↓24%	Sofosbuvir was administered irrespective of meals in Phase III trials	Sofosbuvir can be administered irrespective of meals
Ledipasvir	High-fat	8	AUC_{inf} ↓44%, C_{max} ↓45%	NA	NA
Ledipasvir and sofosbuvir (fixed-dose combination)	High-fat	28	Ledipasvir: AUC_{inf} ↔, C_{max} ↓12%; Sofosbuvir: AUC_{inf} ↑79%, C_{max} ↑15%; GS-331007: AUC_{inf} ↑12%, C_{max} ↓30%	The fixed-dose combination of ledipasvir and sofosbuvir was administered irrespective of meal intake in Phase III trials	The fixed-dose combination of ledipasvir and sofosbuvir can be administered irrespective of meals
	Moderate-fat	29	Ledipasvir: AUC_{inf} ↑15%, C_{max}↑9%; Sofosbuvir: AUC_{inf} ↑95%, C_{max} ↑26%; GS-331007: AUC_{inf} ↑17%, C_{max} ↓18%		
Sofosbuvir and velpatasvir (fixed-dose combination)	High-fat (800 kcal, 50% kcal from fat)	30	Velpatasvir: AUC_{inf} ↑21%, C_{max} ↔; Sofosbuvir: AUC_{inf} ↑78%, C_{max}↓11%; GS-331007: AUC_{inf} ↔, C_{max} ↓37%	The fixed-dose combination of velpatasvir and sofosbuvir was administered irrespective of meals in Phase III trials	The fixed-dose combination of velpatasvir and sofosbuvir can be administered irrespective of meals
	Moderate-fat (600 kcal, 30% kcal from fat)	30	Velpatasvir: AUC_{inf} ↑34%, C_{max}↑31%; Sofosbuvir: AUC_{inf} ↑60%, C_{max}↓5%; GS-331007: AUC_{inf} ↔, C_{max} ↓25%		
Sofosbuvir/velpatasvir (400/100 mg) + voxilaprevir (100 mg)	Low-fat (400 kcal, 10% kcal from fat)	15	Velpatasvir: AUC_{inf} ↑166%, C_{max} ↑187%; Voxilaprevir: AUC_{inf} ↑112%, C_{max} ↑147%; Sofosbuvir: AUC_{inf} ↑118%, C_{max} ↑73%; GS-331007: AUC_{inf} ↑13%, C_{max} ↓19%	NA	The combination of voxilaprevir plus sofosbuvir/velpatasvir should be administered with food in the subsequent Phase II and III trials to circumvent the potential loss of systemic exposures of voxilaprevir and velpatasvir under fasting conditions
	Moderate-fat (600 kcal, 27% kcal from fat)	15	Velpatasvir: AUC_{inf} ↑129%, C_{max} ↑146%; Voxilaprevir: AUC_{inf} ↑185%, C_{max} ↑259%; Sofosbuvir: AUC_{inf} ↑144%, C_{max} ↑76%; GS-331007: AUC_{inf} ↑13%, C_{max} ↓24%		
Sofosbuvir, velpatasvir and voxilaprevir (fixed-dose combination)	High-fat (1000 kcal, 45–55% kcal from fat)	34	Velpatasvir: AUC_{inf} ↑40%, C_{max} ↑37%; Voxilaprevir: AUC_{inf} ↑435%, C_{max} ↑680%; Sofosbuvir: AUC_{inf} ↑64%, C_{max} ↔; GS-331007: AUC_{inf} ↔, C_{max} ↓35%	The fixed-dose combination of sofosbuvir/velpatasvir/voxilaprevir (400/100/100 mg) with food was implemented in Phase III trials and sufficient effectiveness and safety were demonstrated	The fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir is recommended to be given with food
Elbasvir and grazoprevir (fixed-dose combination)	High-fat (900 kcal, 500 kcal from fat)	26	Elbasvir: AUC_{inf} ↓11%, C_{max}↓15%; Grazoprevir: AUC_{inf} ↑54%, C_{max} ↑183%	The fixed-dose combination of elbasvir and grazoprevir was administered irrespective of meals in Phase III trials	The fixed-dose combination of elbasvir and grazoprevir can be administered irrespective of meals
Simeprevir	High-fat (928 kcal)	24	AUC_{inf} ↑61%, C_{max} ↑49%	Although simeprevir was administered irrespective of meals in Phase III trials, the majority of simeprevir doses were reported to be taken with a meal	Simeprevir should be administered with a meal, without regard to meal compositions in terms of fat or calorie content
	Low-to-moderate (533 kcal)	24	AUC_{inf} ↑69%, C_{max} ↑60%		
Ombitasvir, paritaprevir, and ritonavir (fixed-dose combination)	High-fat (850–900 kcal, 60% kcal from fat)	18	Ombitasvir: AUC_{inf} ↑76%, C_{max} ↑106%; Paritaprevir: AUC_{inf} ↑180%, C_{max} ↑300%; Ritonavir: AUC_{inf} ↑44%, C_{max} ↑50%	The fixed-dose combination of ombitasvir, paritaprevir and ritonavir was administered with a meal in Phase III trials	The fixed-dose combination of ombitasvir, paritaprevir and ritonavir should be given with a meal irrespective of fat or calorie content
	Moderate-fat (600 kcal, 20–30% kcal from fat)	18	Ombitasvir: AUC_{inf} ↑82%, C_{max} ↑127%; Paritaprevir: AUC_{inf} ↑211%, C_{max}↑367%; Ritonavir: AUC_{inf} ↑49%, C_{max} ↑63%		

TABLE 2 (*Continued*)

DAA medication	Meal type	N	Changes in pharmacokinetics[a]	Meal intake in Phase III trials	Recommendations
Dasabuvir	High-fat (850–900 kcal, 60% kcal from fat)	17	Dasabuvir: AUC_{inf} ↑22%, C_{max} ↑42%; Dasabuvir M1: AUC_{inf} ↑11%, C_{max} ↑17%	Dasabuvir was administered under fed conditions in Phase III trials	Dasabuvir should be taken with a meal regardless of fat or calorie content
	Moderate-fat (600 kcal, 20–30% kcal from fat)	17	Dasabuvir: AUC_{inf} ↑30%, C_{max} ↑53%; Dasabuvir M1: AUC_{inf} ↑30%, C_{max} ↑50%		
Glecaprevir and pibrentasvir (fixed-dose combination)	High-fat (~850 kcal, 51% kcal from fat)	38	Glecaprevir: AUC_{inf} ↑83%, C_{max} ↑114%; Pibrentasvir: AUC_{inf} ↑53%, C_{max} ↑105%;	The fixed-dose combination of glecaprevir and pibrentasvir was administered with food without regard to fat or calorie content in Phase III trials	The fixed-dose combination of glecaprevir and pibrentasvir should be given with a meal irrespective of the content of fat or calories
	Moderate-fat (673 kcal, ~30% kcal from fat)	38	Glecaprevir: AUC_{inf} ↑163%, C_{max} ↑216%; Pibrentasvir: AUC_{inf} ↑40%, C_{max} ↑90%;		

Abbreviations: AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; C_{max}, peak plasma concentration.
[a] All studies were conducted in healthy subjects.

omeprazole 20 mg per day while being treated with ledipasvir/sofosbuvir.

Sofosbuvir/velpatasvir

Sofosbuvir/velpatasvir is a fixed-dose, sofosbuvir-based DAA combination of 400 mg sofosbuvir and 100 mg velpatasvir. Velpatasvir has an aqueous solubility >36 mg/ml at pH 1.2, and a dramatically lower solubility <0.1 mg/ml at pH higher than 5 (Table 1) [19,20]. In addition to the pH-dependent solubility profile, velpatasvir at the clinical dose level of 100 mg would no longer be soluble in a 250 ml aliquot of buffers under near-neutral pH conditions. Sofosbuvir/velpatasvir is therefore considered susceptible to gastric-acid-related DDIs on the basis of these *in vitro* observations.

Like sofosbuvir, sofosbuvir/velpatasvir can be given regardless of meal intake because of the absence of clinically significant changes in systemic and peak exposure of either velpatasvir or GS-331007, in the presence of different types of meals (Table 2) [19,20]. Dedicated DDI studies for assessing the risk of compromised velpatasvir exposure in subjects with pharmaceutical-induced achlorhydria were conducted in the absence and presence of food [19,20]. Velpatasvir exposure was decreased greatly by >50% when administered as a single agent under fasted conditions simultaneously with omeprazole 20 mg once daily (Table 3). Similarly, an ~40% reduction in systemic and peak velpatasvir exposures was observed in the presence of a steady-state level of omeprazole when administered as sofosbuvir/velpatasvir without food (Table 3). Furthermore, the use of omeprazole (20 mg) with sofosbuvir/velpatasvir under fasted conditions in a staggered manner did not attenuate the degree of DDIs (Table 3). Instead, administration of sofosbuvir/velpatasvir under fed conditions and 4 h before omeprazole 20 mg decreased systemic velpatasvir exposure only by 26%, thereby informing the mitigation strategy of drug interactions between sofosbuvir/velpatasvir and PPIs (Table 3). Nevertheless, a similar strategy failed to show the ability to overcome the effect of concurrent omeprazole at a higher dose level of 40 mg once daily. By contrast, a modified schedule with a shorter time of staggered dosing (i.e., taking sofosbuvir/velpatasvir under fed conditions and 2 h after 20 mg omeprazole) did not lead to an unimpaired bioavailability of velpatasvir as well (Table 3). On the basis of these findings, concurrent PPI use is generally not recommended if treatment with PPI is not deemed clinically necessary; otherwise, patients should be fully educated to ensure sofosbuvir/velpatasvir is administered with a meal and staggered 4 h before treatment with 20 mg omeprazole.

Alternative strategies for mitigating gastric-acid-associated DDIs with sofosbuvir/velpatasvir have also been developed based on results from DDI trials conducted with famotidine [20]. In two dedicated DDI studies with velpatasvir, velpatasvir bioavailability was not compromised when given fasting with famotidine 20 mg in either a simultaneous or staggered manner (Table 3). Likewise, velpatasvir exposure was modified slightly by <20% when administered as sofosbuvir/velpatasvir under fasted conditions with 40 mg famotidine in either a simultaneous or staggered manner (Table 3). As indicated, sofosbuvir/velpatasvir could be given with famotidine (≤40 mg), regardless of the timing of sofosbuvir/velpatasvir administration with reference to famotidine.

Sofosbuvir/velpatasvir/voxilaprevir

Sofosbuvir/velpatasvir/voxilaprevir is a fixed-dose, sofosbuvir-based DAA combination of 400 mg sofosbuvir, 100 mg velpatasvir and 100 mg voxilaprevir. In view of the potential for suboptimal plasma levels of velpatasvir because of inappropriate coadministration of sofosbuvir/velpatasvir with a PPI, dedicated DDI investigations using sofosbuvir/velpatasvir/voxilaprevir co-treated with omeprazole or famotidine were performed in parallel [21]. Sofosbuvir/velpatasvir/voxilaprevir was taken with a meal in all these DDI studies to account for the positive impact of food on the bioavailability of velpatasvir and voxilaprevir under clinically relevant scenarios (Tables 2 and 3) [21]. Omeprazole (20 mg) was dosed in a staggered manner with sofosbuvir/velpatasvir/voxilaprevir (i.e., either 2 h before or 4 h post sofosbuvir/velpatasvir/voxilaprevir administration). Both staggered dosing regimens resulted in ~50% decrease in velpatasvir exposure with a <25% decrease in systemic and peak levels of voxilaprevir and GS-331007, relative to those of sofosbuvir/velpatasvir/voxilaprevir administered alone (Table 3) [21,22]. Nevertheless, given that velpatasvir exposure after receiving a single dose of sofosbuvir/velpatasvir/voxilaprevir is already twofold greater than after sofosbuvir/velpatasvir dosing, a 50% lower velpatasvir exposure associated with the co-therapy of sofosbuvir/velpatasvir/voxilaprevir with omeprazole is unlikely to be of clinical importance. In other words, coadministration of sofosbuvir/velpatasvir/voxilaprevir with 20 mg omeprazole has been shown to provide systemic velpatasvir exposure matching that of sofosbuvir/velpatasvir ad-

TABLE 3

Dedicated drug–drug interaction (DDI) studies for assessing gastric-acid-mediated DDIs with direct-acting antiviral (DAA) drugs[a] [7–10,14,15,17–25,27–30,37–40]

DAA medication	Acid-reducing agent	Treatment regimen	Study design (timing of administration)	N	Changes in DAA drug pharmacokinetics
Daclatasvir	PPI: pmeprazole	Multiple-dose omeprazole (40 mg) + single-dose drug (20 mg)	Concomitant dosing: omeprazole QD for 5 days before concurrent use of daclatasvir on day 6	11	AUC_{inf} ↔ C_{max} ↓20%
		Multiple-dose omeprazole (40 mg) + single-dose drug (60 mg)	Concomitant dosing: omeprazole QD for 5 days before concurrent use of daclatasvir on day 6	11	AUC_{inf} ↓16% C_{max} ↓36%
	H2-antagonist: famotidine	Single-dose famotidine (40 mg) under fasted conditions + single-dose drug (60 mg) under fasted conditions	Staggered dosing: daclatasvir administered 2 h after famotidine	18	AUC_{inf} ↓18% C_{max} ↓44%
Ledipasvir	PPI: omeprazole	Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (30 mg) with a meal	Staggered dosing: omeprazole QD for 6 days followed by ledipasvir administered 2 h after the last omeprazole dose	16	AUC_{inf} ↓42% C_{max} ↓48%
Ledipasvir and sofosbuvir (fixed-dose combination)	PPI: omeprazole	Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (ledipasvir/sofosbuvir 90/400 mg) under fasted conditions	Concomitant dosing: omeprazole QD for 6 days plus ledipasvir/sofosbuvir administered simultaneously with the last dose of omeprazole	16	Ledipasvir: AUC_{inf} ↔, C_{max} ↓11%; Sofosbuvir: AUC_{inf} ↔, C_{max} ↑12%; GS-331007: AUC_{inf} ↔, C_{max} ↑14%
	H2-antagonist: famotidine	Single-dose famotidine (40 mg) with a meal + single-dose drug (ledipasvir/sofosbuvir 90/400 mg) with a meal	Concomitant dosing: ledipasvir/sofosbuvir administered simultaneously with famotidine	12	Ledipasvir: AUC_{inf} ↓11%, C_{max} ↓20%; Sofosbuvir: AUC_{inf} ↑11%, C_{max} ↑15%; GS-331007: AUC_{inf} ↔, C_{max} ↔
		Single-dose famotidine (40 mg) with a meal + single-dose drug (ledipasvir/sofosbuvir 90/400 mg) with a meal	Staggered dosing: famotidine administered 12 h before ledipasvir/sofosbuvir	12	Ledipasvir: AUC_{inf} ↔, C_{max} ↓17%; Sofosbuvir: AUC_{inf} ↔, C_{max} ↔; GS-331007: AUC_{inf} ↔, C_{max} ↑13%
Velpatasvir	PPI: omeprazole	Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (100 mg) under fasted conditions	Concomitant dosing: omeprazole QD for 5 days followed by velpatasvir administered simultaneously with omeprazole on day 6	24	AUC_{inf} ↓53% C_{max} ↓55%;
	H2-antagonist: famotidine	Single-dose famotidine (20 mg) under fasted conditions + single-dose drug (100 mg) under fasted conditions	Concomitant dosing: velpatasvir administered simultaneously with famotidine	24	AUC_{inf} ↓9% C_{max} ↓14%
		Single-dose famotidine (20 mg) with a meal + single-dose drug (100 mg) under fasted conditions	Staggered dosing: famotidine administered 12 h before velpatasvir	24	AUC_{inf} ↓8% C_{max} ↓10%

TABLE 3 (*Continued*)

DAA medication	Acid-reducing agent	Treatment regimen	Study design (timing of administration)	N	Changes in DAA drug pharmacokinetics
Sofosbuvir and velpatasvir (fixed-dose combination)	PPI: omeprazole	Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (sofosbuvir/velpatasvir 400/100 mg) under fasted conditions	Concomitant dosing: omeprazole QD for 5 days followed by sofosbuvir/velpatasvir administered simultaneously with omeprazole on day 6	60	Velpatasvir: AUC_{inf} ↓36%, C_{max} ↓37%; Sofosbuvir: AUC_{inf} ↓29%, C_{max} ↓34%; GS-331007: AUC_{inf} ↔, C_{max} ↑18%
		Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (sofosbuvir/velpatasvir 400/100 mg) under fasted conditions	Staggered dosing: omeprazole QD for 6 days followed by sofosbuvir/velpatasvir administered 12 h post the last dose of omeprazole	60	Velpatasvir: AUC_{inf} ↓55%, C_{max} ↓57%; Sofosbuvir: AUC_{inf} ↓44%, C_{max} ↓45%; GS-331007: AUC_{inf} ↔, C_{max} ↑26%
		Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (sofosbuvir/velpatasvir 400/100 mg) with a meal	Staggered dosing: omeprazole QD for 6 days followed by sofosbuvir/velpatasvir administered 2 h post the last dose of omeprazole	40	Velpatasvir: AUC_{inf} ↓38%, C_{max} ↓48%; Sofosbuvir: AUC_{inf} ↔, C_{max} ↓16%; GS-331007: AUC_{inf} ↔, C_{max} ↔
		Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (sofosbuvir/velpatasvir 400/100 mg) with a meal	Staggered dosing: omeprazole QD for 6 days plus sofosbuvir/velpatasvir administered 4 h before the last dose of omeprazole	38	Velpatasvir: AUC_{inf} ↓26%, C_{max} ↓33%; Sofosbuvir: AUC_{inf} ↔, C_{max} ↓21%; GS-331007: AUC_{inf} ↔, C_{max} ↔
		Multiple-dose omeprazole (40 mg) under fasted conditions + single-dose drug (sofosbuvir/velpatasvir 400/100 mg) with a meal	Staggered dosing: omeprazole QD for 6 days plus sofosbuvir/velpatasvir administered 4 h before the last dose of omeprazole	40	Velpatasvir: AUC_{inf} ↓53%, C_{max} ↓56%; Sofosbuvir: AUC_{inf} ↔, C_{max} ↓30%; GS-331007: AUC_{inf} ↔, C_{max} ↔
	H2-antagonist: famotidine	Single-dose famotidine (40 mg) under fasted conditions + single-dose drug (sofosbuvir/velpatasvir 400/100 mg) under fasted conditions	Concomitant dosing: sofosbuvir/velpatasvir administered simultaneously with famotidine	60	Velpatasvir: AUC_{inf} ↓19%, C_{max} ↓20%; Sofosbuvir: AUC_{inf} ↓17%, C_{max} ↔; GS-331007: AUC_{inf} ↔, C_{max} ↓16%
		Single-dose famotidine (40 mg) with a meal + single-dose drug (sofosbuvir/velpatasvir 400/100 mg) under fasted conditions	Staggered dosing: famotidine administered 12 h before sofosbuvir/velpatasvir	60	Velpatasvir: AUC_{inf} ↓15%, C_{max} ↓13%; Sofosbuvir: AUC_{inf} ↓20%, C_{max} ↓23%; GS-331007: AUC_{inf} ↔, C_{max} ↑20%

TABLE 3 (*Continued*)

DAA medication	Acid-reducing agent	Treatment regimen	Study design (timing of administration)	N	Changes in DAA drug pharmacokinetics
Sofosbuvir, velpatasvir and voxilaprevir (fixed-dose combination)	PPI: omeprazole	Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (sofosbuvir/velpatasvir/voxilaprevir 400/100/100 mg) with food	Staggered dosing: omeprazole QD for 6 days followed by sofosbuvir/velpatasvir/voxilaprevir administered 2 h post the last dose of omeprazole	34	Velpatasvir: AUC_{inf} ↓54%, C_{max} ↓57%; Voxilaprevir: AUC_{inf} ↔, C_{max} ↓24%; Sofosbuvir: AUC_{inf} ↓27%, C_{max} ↓23%; GS-331007: AUC_{inf} ↔, C_{max} ↔
		Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (sofosbuvir/velpatasvir/voxilaprevir 400/100/100 mg) with food	Staggered dosing: omeprazole QD for 6 days followed by sofosbuvir/velpatasvir/voxilaprevir administered 4 h before the last dose of omeprazole	34	Velpatasvir: AUC_{inf} ↓51%, C_{max} ↓51%; Voxilaprevir: AUC_{inf} ↔, C_{max} ↔; Sofosbuvir: AUC_{inf} ↔, C_{max} ↔; GS-331007: AUC_{inf} ↔, C_{max} ↔
	H2-antagonist: famotidine	Single-dose famotidine (40 mg) with food + single-dose drug (sofosbuvir/velpatasvir/voxilaprevir 400/100/100 mg) with food	Concomitant dosing: sofosbuvir/velpatasvir/voxilaprevir administered simultaneously with famotidine	35	Velpatasvir: AUC_{inf} ↔, C_{max} ↔; Voxilaprevir: AUC_{inf} ↔, C_{max} ↔; Sofosbuvir: AUC_{inf} ↔, C_{max} ↔; GS-331007: AUC_{inf} ↔, C_{max} ↔
		Single-dose famotidine (40 mg) with food + single-dose drug (sofosbuvir/velpatasvir/voxilaprevir 400/100/100 mg) with food	Staggered dosing: famotidine administered 12 h before sofosbuvir/velpatasvir/voxilaprevir	36	Velpatasvir: AUC_{inf} ↔, C_{max} ↔; Voxilaprevir: AUC_{inf} ↔, C_{max} ↔; Sofosbuvir: AUC_{inf} ↔, C_{max} ↔; GS-331007: AUC_{inf} ↔, C_{max} ↔
Elbasvir and grazoprevir (fixed-dose combination)	PPI: pantoprazole	Multiple-dose pantoprazole (40 mg) under fasted conditions + single-dose drug (elbasvir/grazoprevir 50 mg/100 mg) under fasted conditions	Staggered dosing: pantoprazole QD for 5 days followed by elbasvir/grazoprevir 2 h after the last dose of pantoprazole	16	Elbasvir: AUC_{inf} ↔, C_{max} ↔; Grazoprevir: AUC_{inf} ↑12%, C_{max} ↑10%
	H2-antagonist: famotidine	Single-dose famotidine (20 mg) under fasted conditions + single-dose drug (elbasvir/grazoprevir 50 mg/100 mg) under fasted conditions	Staggered dosing: elbasvir/grazoprevir administered 12 h after famotidine	16	Elbasvir: AUC_{inf} ↔, C_{max} ↑11%; Grazoprevir: AUC_{inf} ↑10%, C_{max} ↓11%
Ombitasvir and paritaprevir/ritonavir (fixed-dose combination)	PPI: omeprazole	Single-dose omeprazole (40 mg) under fed conditions + multiple-dose drug (ombitasvir/paritaprevir/ritonavir 25/150/100 mg) under fed conditions	Concomitant dosing: ombitasvir/paritaprevir/ritonavir QD plus omeprazole administered simultaneously with the last dose of ombitasvir/paritaprevir/ritonavir	12	Ombitasvir: $AUC_{\tau,ss}$ ↔, $C_{max,ss}$ ↔, C_{trough} ↔; Paritaprevir: $AUC_{\tau,ss}$ ↑8%, $C_{max,ss}$ ↑18%, C_{trough} ↔
		Multiple-dose omeprazole (40 mg) under fasted conditions + multiple-dose drug (ombitasvir/paritaprevir/ritonavir 25/150/100 mg) under fed conditions	Staggered dosing: ombitasvir/paritaprevir/ritonavir QD plus omeprazole QD administered 1.5 h before ombitasvir/paritaprevir/ritonavir	12	Ombitasvir: $AUC_{\tau,ss}$ ↔, $C_{max,ss}$ ↔, C_{trough} ↔; Paritaprevir: $AUC_{\tau,ss}$ ↓7%, $C_{max,ss}$ ↔, C_{trough} ↓17%

TABLE 3 (*Continued*)

DAA medication	Acid-reducing agent	Treatment regimen	Study design (timing of administration)	N	Changes in DAA drug pharmacokinetics
Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	PPI: omeprazole	Single-dose omeprazole (40 mg) under fed conditions + multiple-dose drug (ombitasvir/paritaprevir/ ritonavir 25/150/100 mg QD and dasabuvir 250 mg BID) under fed conditions	Concomitant dosing: ombitasvir/paritaprevir/ritonavir QD and dasabuvir BID plus omeprazole administered simultaneously with the last dose of ombitasvir/paritaprevir/ritonavir	11	Ombitasvir: $AUC_{\tau,ss}$ ↔, $C_{max,ss}$ ↔, C_{trough} ↔; Paritaprevir: $AUC_{\tau,ss}$ ↔, $C_{max,ss}$ ↔, C_{trough} ↑16%; Ritonavir: $AUC_{\tau,ss}$ ↔, $C_{max,ss}$ ↔, C_{trough} ↔; Dasabuvir: $AUC_{\tau,ss}$ ↔, $C_{max,ss}$ ↓5%, C_{trough} ↔; Dasabuvir M1: $AUC_{\tau,ss}$ ↔, $C_{max,ss}$ ↔, C_{trough} ↓5%
		Multiple-dose omeprazole (40 mg) under fasted conditions + multiple-dose drug (ombitasvir/paritaprevir/ ritonavir 25/150/100 mg QD and dasabuvir 250 mg BID) under fed conditions	Staggered dosing: ombitasvir/paritaprevir/ritonavir QD and dasabuvir BID plus omeprazole QD administered ~1.5 h before ombitasvir/ paritaprevir/ritonavir	11	Ombitasvir: $AUC_{\tau,ss}$ ↔, $C_{max,ss}$ ↔, C_{trough} ↔; Paritaprevir: $AUC_{\tau,ss}$ ↑18%, $C_{max,ss}$ ↑19%, C_{trough} ↓8%; Dasabuvir: $AUC_{\tau,ss}$ ↑13%, $C_{max,ss}$ ↑8%, C_{trough} ↑5%; Dasabuvir M1: $AUC_{\tau,ss}$ ↔, $C_{max,ss}$ ↑5%, C_{trough} ↔
Glecaprevir and pibrentasvir (fixed-dose combination)	PPI: omeprazole	Multiple-dose omeprazole (20 mg) under fasted conditions + single-dose drug (glecaprevir/pibrentasvir 300/120 mg) under fed conditions	Staggered dosing: omeprazole QD before breakfast for 6 days followed by glecaprevir/pibrentasvir with breakfast	12	Glecaprevir: AUC_{last} ↓29%, C_{max} ↓22%; Paritaprevir: AUC_{last} ↔, C_{max} ↔
		Multiple-dose omeprazole (40 mg) under fasted conditions + single-dose drug (glecaprevir/pibrentasvir 300/120 mg) under fed conditions	Staggered dosing: omeprazole QD before breakfast for 6 days followed by glecaprevir/pibrentasvir with breakfast	12	Glecaprevir: AUC_{last} ↓51%, C_{max} ↓64%; Paritaprevir: AUC_{last} ↔, C_{max} ↔
		Multiple-dose omeprazole (40 mg) under fasted conditions + single-dose drug (glecaprevir/pibrentasvir 300/120 mg) under fed conditions	Staggered dosing: omeprazole QD in the evening for 5 days followed by glecaprevir/pibrentasvir in the morning of the 6th day	12	Glecaprevir: AUC_{last} ↓49%, C_{max} ↓46%; Paritaprevir: AUC_{last} ↔, C_{max} ↔

Abbreviations: AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve from time zero to time of last measurable concentration; $AUC_{\tau,ss}$, area under the plasma concentration-time curve during a dosing interval at steady state; BID, twice daily; C_{max}, peak plasma concentration; $C_{max,ss}$, peak plasma concentration during a dosing interval at steady state; C_{trough}, trough plasma concentration; PPI, proton-pump inhibitor; QD, once daily.

[a] All studies were conducted in healthy subjects.

ministered alone [21,22], implying the absence of clinically meaningful interactions between sofosbuvir/velpatasvir/voxilaprevir and omeprazole (20 mg). Consequently, sofosbuvir/velpatasvir/voxilaprevir should be taken with a meal and staggered from omeprazole or other PPIs at a dose level being comparable with omeprazole 20 mg if necessary.

Additionally, concurrent use of sofosbuvir/velpatasvir/voxilaprevir with famotidine 40 mg in either a simultaneous or staggered manner under nonfasting conditions did not affect pharmacokinetic exposures of velpatasvir, voxilaprevir, sofosbuvir and GS-331007 [22]. Thus, famotidine or other H2 antagonists at therapeutic dose could be co-prescribed with sofosbuvir/velpatasvir/voxilaprevir in clinical practice, from a clinical pharmacology perspective.

Elbasvir/grazoprevir

Elbasvir/grazoprevir is a fixed-dose DAA combination with both components exhibiting pH-dependent solubility (Table 1). At the approved dose of 50 mg elbasvir and 100 mg grazoprevir, elbasvir and grazoprevir are practically insoluble in water. Owing to the acidic nature of grazoprevir, coadministration with acid-reducing agents is not likely to modify its absorption to a clinically significant degree. Dissimilarly, elbasvir is a weak base with a lower solubility at a higher pH (i.e., 0.05 mg/l at pH 5, 0.008 mg/l at pH 7 and 0.02 mg/l at pH 9) [23,24], suggesting the possibility of gastric-acid-related DDIs for elbasvir/grazoprevir.

Administration of elbasvir/grazoprevir with a high-fat meal resulted in an 11% and 15% decrease in systemic and peak elbasvir exposure, respectively [24]. However, in the presence of high-fat food, systemic grazoprevir exposure was increased >50% compared with that in the absence of food [24]. Although increases in grazoprevir absorption and exposure were clearly seen, the food effects on grazoprevir and elbasvir are not considered clinically relevant based on the exposure–response relationship for drug safety and efficacy according to the regulatory review [24,25].

A dedicated DDI study for assessing the influence of co-therapy of elbasvir/grazoprevir and acid-reducing agents was performed under fasted conditions. Pharmacokinetic exposures were comparable following a single-dose administration of elbasvir/grazoprevir with or without coadministration of the PPI pantoprazole (40 mg) or a 20 mg single dose of the H2 antagonist famotidine [23]. Elbasvir bioavailability was not influenced by 5-day once-daily administration of pantoprazole in the fasted state (Table 3). Furthermore, grazoprevir absorption and exposure were modified only slightly by <20% after staggered dosing of pantoprazole (Table 3). Likewise, treatment with famotidine in the evening and 2 h before elbasvir/grazoprevir dosing affected peak and systemic exposure of either elbasvir or grazoprevir only by <15%. In view of these findings, elbasvir/grazoprevir can be given fasting preferably 2 h post PPI dosing, from a DDI standpoint. Instead, H2 antagonists or antacids can be considered as an alternative to PPIs.

It is worth mentioning that PPIs, either alone or involved as an interaction term with other factors, were not found to be a predictor for SVR12 rates on the basis of *post hoc* subgroup analysis using data generated from six Phase III trials [26]. Moreover, secondary population pharmacokinetic analysis using data from five of these Phase III trials indicated similar peak or systemic elbasvir exposure at steady-state regardless of consistent baseline PPI use, confirming that concomitant PPI treatment did not lead to a significant loss of the efficacy of elbasvir/grazoprevir [26].

Simeprevir

Simeprevir is a weak base with a pH-independent solubility, which is practically insoluble in aqueous media throughout the entire physiological pH range [27,28]. The maximum amount of aqueous-soluble simeprevir is much less than the dose strength of 150 mg over pH range 1.0–7.5. On the basis of the pH-independent solubility profile determined *in vitro*, a pronounced effect of acid-reducing agents on simeprevir bioavailability is not likely, although no clinical studies have been done to examine the interactions between acid-reducing agents and simeprevir. As such, the co-prescription of simeprevir with acid-reducing agents is not contraindicated.

After a single dose of 150 mg of simeprevir, ~50% interindividual variability of AUC and C_{max} in the fasted state was identified. Compared with the results under fasted conditions, AUC_{inf} and C_{max} of simeprevir were increased when administered after either a high-fat or low-to-moderate breakfast (Table 2) [27]. The increases in simeprevir AUC_{inf} are 61% or 69% under high-fat or low-to-moderate-fat conditions, respectively, which did not fall within the variability range of ACU_{inf} under fasted conditions, implying a clinically significant food effect (Table 2). Moreover, it was observed that simeprevir AUC_{inf} was influenced by high-fat as well as low-to-moderate-fat food analogously, indicating food type had no influence on systemic simeprevir exposure. Although simeprevir was administered without regard to food in Phase III trials, the large majority of simeprevir doses were documented as being given with a meal [27]. Because the dosing schedule implemented in Phase III trials serves as the basis for dosing recommendations on drug administration with respect to food intake, simeprevir should be administered with a meal irrespective of the content of fat or calories. Simeprevir is therefore advised to be taken under nonfasting conditions when coadministered with acid-reducing agents from clinical pharmacology perspectives.

Ombitasvir/paritaprevir/ritonavir

Ombitasvir/paritaprevir/ritonavir is a fixed-dose DAA combination of ombitasvir (25 mg), paritaprevir (150 mg) and ritonavir (100 mg), a cytochrome P450 (CYP3A) inhibitor served as a bioavailability enhancer of paritaprevir, also known as the 2D regimen [29]. Ombitasvir and paritaprevir have very poor solubilities under either acidic or neutral conditions [29,30], whereas ritonavir shows pH-dependent solubility characteristics with an extremely low solubility of ~1 μg/ml at pH 6.8 and a several-hundred-times higher solubility of 400 μg/ml at pH 1 (Table 1) [31–33]. Obviously, ritonavir is poorly soluble in the biorelevant volume of 250 ml at near-neutral pH levels. On the basis of these *in vitro* observations, the 2D regimen is probably sensitive to gastric-acid-associated DDIs perpetrated by acid-reducing agents.

Systemic exposure to ombitasvir and paritaprevir was significantly elevated by ~80% and 200%, respectively, in the presence of either a high-fat or moderate-fat meal (Table 2) [30]. Because of the improved exposure of ombitasvir and paritaprevir with food, subsequent Phase I–III trials have been performed under fed conditions [34–36]. In the DDI studies with omeprazole, the 2D regimen was given with food, whereas omeprazole was dosed with

or without food [37]. All the steady-state systemic peak and trough exposures of ombitasvir and paritaprevir in the presence of omeprazole (a single dose of 40 mg or 40 mg once-daily) fell within the bioequivalence boundaries of 80–125% of those in the absence of omeprazole (Table 3) [37], demonstrating the lack of clinically meaningful DDIs between the 2D regimen and omeprazole. Hence, no restrictions should be required on the collaborative use of the 2D regimen with omeprazole or other acid-reducing agents.

Ombitasvir/paritaprevir/ritonavir and dasabuvir

Ombitasvir, paritaprevir (boosted with co-dosed ritonavir) and dasabuvir are collectively known as the 3D regimen used with or without ribavirin for the treatment of chronic HCV genotype 1a or 1b infection. Similar to the 2D regimen, pronounced effects of meals on dasabuvir bioavailability were observed (Table 2) [38]. In the DDI studies with omeprazole, the 3D regimen was therefore administered under nonfasting conditions following co-dosing with either a single oral dose of 40 mg omeprazole or omeprazole 40 mg once-daily [37]. In the coadministration scenarios, all exposure metrics in terms of $AUC_{\tau,ss}$, $C_{max,ss}$ and C_{trough} of ombitasvir, paritaprevir, dasabuvir and its predominant metabolite dasabuvir M1 were unaltered by omeprazole. Like the 2D regimen, the 3D regimen with food can generally be coadministered with PPIs or other acid-reducing agents in the indicated patients without being subjected to clinically meaningful DDIs associated with reduced gastric acidity.

Of note, rates of SVR12 have been shown to be high irrespective of PPI usage or the PPI dosage in a *post hoc* analysis based on data from 2035 patients with HCV genotype 1 infection in the efficacy cohorts within six Phase III trials of the 3D regimen with or without ribavirin [1]. Moreover, concurrent use of the 3D regimen with PPIs was not associated with lower rates of SVR12 nor virologic failure. The results of the retrospective assessment are in line with those of prospective DDI studies, supporting the concomitant use of PPIs or other acid-reducing agents with ombitasvir/paritaprevir/ritonavir plus dasabuvir.

Glecaprevir/pibrentasvir

Glecaprevir/pibrentasvir is a fixed-dose combination of two new generation DAAs: 100 mg glecaprevir and 40 mg pibrentasvir. Glecaprevir displays a pH-dependent solubility, being practically insoluble as long as the pH is lower than 5.1 and very slightly soluble at pH >6.6 with a solubility of ~0.63 mg/ml [39,40]. The solubility of pibrentasvir also depends on the media pH, which is ~0.9 mg/ml at pH 1.1 and <0.6 mg/ml as long as the pH is higher than 2.1 [39,40]. On the basis of the FDA-proposed preliminary framework [11], pibrentasvir was anticipated to have gastric-acid-related DDI liability.

Administration of glecaprevir/pibrentasvir with a moderate-fat meal could lead to increased AUC_{inf} ratios (fed:fasting) of 2.63 [90% confidence interval (CI): 2.18–3.17] and 1.40 (90% CI: 1.11–1.78) for glecaprevir and pibrentasvir, respectively [41]. Following a high-fat meal, AUC_{inf} ratios between fed and fasted conditions for glecaprevir and pibrentasvir are 1.83 (90% CI: 1.52–2.20) and 1.53 (90% CI: 1.20–1.95), respectively (Table 2) [40]. Given the significantly increased exposures of glecaprevir and pibrentasvir with either a moderate-fat or high-fat meal, glecaprevir/pibrentasvir was taken with a meal regardless of fat or calorie content in Phase III trials [40,41]. Glecaprevir/pibrentasvir is therefore recommended to be administered with food.

For glecaprevir and pibrentasvir, dedicated DDI studies with acid-reducing agents were conducted in the fed state [39,40]. No clinically significant changes in plasma peak concentration and overall exposure of glecaprevir and pibrentasvir were observed when omeprazole 20 mg once-daily was used with a single-dose of glecaprevir/pibrentasvir. However, a profound reduction by >50% was observed for glecaprevir in response to 40 mg of omeprazole once-daily (Table 3). Furthermore, staggering the dosing of glecaprevir/pibrentasvir and 40 mg omeprazole by 12 h did not mitigate the degree of such DDIs. Thus, glecaprevir/pibrentasvir can be given with omeprazole at a low dose of 20 mg, whereas use of omeprazole at a high dose of 40 mg should be avoided owing to the potential risk of suboptimal glecaprevir exposure. Interestingly, based on glecaprevir solubility profile observed *in vitro*, glecaprevir was not expected to be susceptible to clinical DDIs with omeprazole. The false-negative DDI predicted outcome might be attributed to dissimilar dissolution characteristics of glecaprevir between *in vivo* and *in vitro* situations, highlighting the difficulty in prediction of gastric-acid-related DDI potential using *in vitro* solubility data alone.

A *post hoc* subgroup analysis of glecaprevir/pibrentasvir treatment collaboratively with PPIs in a Phase III trial showed that 30 (97%) of the 31 patients who were coadministered PPIs achieved SVR at 12 weeks [41]. However, data for all PPIs in the *post hoc* analysis were pooled together instead of stratifying those data by the dose, dosing schedule and duration of the concomitant PPI, rendering the results inconclusive [42]. Based on current evidence, we may not recommend taking glecaprevir/pibrentasvir concurrently with omeprazole 40 mg once-daily in routine clinical practice unless the expected benefit outweighs the potential risk.

Development of strategies to mitigate drug interactions caused by concurrent acid-suppression therapy: current perspectives

Prospective DDI studies for concomitant DAA and acid-suppression therapy serve as the basis of strategies to potentially circumvent such interactions with appropriate dosing regimens or alternative acid-suppression therapy. Given that PPIs share some similar effects to food on gastrointestinal physiology such as increasing luminal pH in the stomach and duodenum and delaying gastric emptying [43–49], assessments of gastric-acid-related DDIs can be confounded by meal intake conditions. For the DAA medicines that can be given with or without food, such DDI studies with a PPI could be done under pre-prandial and/or post-prandial scenarios. For example, the DDIs with a PPI for ledipasvir or velpatasvir were explored in the absence as well as the presence of a meal, whereas the possibility of such DDIs for elbasvir/grazoprevir was only studied under fasted conditions. Given that the impact of meals on the degree of such DDIs appeared to be unpredictable, for a DAA drug where fasting bioavailability has been shown to be diminished under conditions of low gastric acidity induced by a PPI, further DDI investigations taking ingestion of a meal into account are warranted, which could facilitate the establishment of strategies to circumvent such interactions. Where administration with food is advised, a meal should first be eaten before administration of the DAA medications in all DDI studies with acid-reducing agents, aiming at assessing the

potential for gastric-acid-related DDIs under clinically relevant conditions, as seen in the cases of sofosbuvir/velpatasvir/voxilaprevir, ombitasvir/paritaprevir/ritonavir, ombitasvir/paritaprevir/ritonavir plus dasabuvir and glecaprevir/pibrentasvir.

When a clinically significant drug interaction with a PPI is identified, subsequent DDI assessments with alternative dosing regimens in terms of a reduced dose of the PPI, the timing of the DAA drug administration in relation to PPI dosing and frequency of PPI use are of value to inform the selection of the most appropriate dosing regimen if use of a PPI is considered medically necessary, as elucidated in the example of sofosbuvir/velpatasvir. Of note, mitigation of the effect of PPIs due to gastric acid suppression on the bioavailability of DAA medications appears to be only achieved by sufficiently considering the dose of the PPI and dosage timing of the PPI in respect to the DAA drug and meal intake, because PPIs are thought to be able to inhibit the gastric acid secretion to the greatest extent among acid-reducing agents. Owing to the short duration of gastric-pH-elevation induced by pretreatment with H2 antagonists relative to PPIs, coadministration of a DAA drug with a H2 antagonist in a staggered manner (e.g., 12 h apart from the DAA medication of interest) could generally be adequate to overcome such DDIs, as shown in the cases of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir and elbasvir/grazoprevir. Similarly, the impact of short-acting antacids (such as aluminum hydroxide and magnesium hydroxide) on the absorption and exposure of a DAA drug is usually considered to be minimal when dosed in a staggered manner with the DAA drug, although there are no data available on concurrent use of the DAA drugs with antacids.

Concluding remarks

Drug interactions between DAA medications and acid-reducing agents as a result of depressed gastric acidity remain a great concern in drug development and treatment [50,51], which could lead to impaired bioavailability and suboptimal plasma concentrations of DAA medicines and subsequently compromised treatment outcomes. However, identification of clinically significant drug interactions associated with elevated gastric pH is not well characterized, particularly in HCV-infected patients receiving DAA therapy. In well-designed, dedicated DDI trials, all confounding factors are balanced and controlled, providing reliable information on drug interactions associated with gastric-acid suppression. By contrast, population pharmacokinetic or *post hoc* subgroup analyses using data derived from Phase II and III studies appear to be more sensitive to check either the presence or absence of clinically relevant gastric-acid-mediated DDIs for DAA drugs, rather than ruling out the presence of such DDIs [42,52,53], which should be viewed as an exploratory assessment rather than level 1 evidence. Priorities for prospective DDI studies for assessment of such interactions in early-phase clinical development are warranted.

A better understanding of the study design of prospective DDI studies for assessing gastric-acid-related DDIs with DAA medications can facilitate the development and establishment of mitigation strategies or dosing guidelines to circumvent such DDIs. Because the extent of gastric-acid-mediated DDIs relies heavily on the class and the dosing regimen of the acid-reducing agent, DDI mitigation strategies could only be established by sufficiently accounting for food intake, the dosage timing of the DAA drug with reference to the PPI used, the dose of the PPI and alternative acid-suppression therapy. Hypothesis-driven physiologically-based pharmacokinetic modeling could be acted as a tool for revealing the underlying mechanisms of such DDIs with a specific DAA medication [54]. Ultimately, physicians and pharmacists should be clearly aware of the potential low rates of SVR owing to DDIs between acid-reducing agents and DAA medicines, especially for sofosbuvir/velpatasvir and ledipasvir/sofosbuvir. Patients should be fully instructed to assure an appropriate dosing regimen when taking DDA medications collaboratively with acid-reducing agents.

Conflicts of interest

Guo Yu, Yi Zheng, Yichao Yu, Guo-Fu Li and Hartmut Derendorf have no conflicts of interest to declare.

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