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REVIEW ARTICLE

Drug–Drug Interactions with the NS3/4A Protease Inhibitor Simeprevir

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Abstract Simeprevir is an NS3/4A protease inhibitor approved for the treatment of hepatitis C infection, as a component of combination therapy. Simeprevir is metabolized by the cytochrome P450 (CYP) system, primarily CYP3A, and is a substrate for several drug transporters, including the organic anion transporting polypeptides (OATPs). It is susceptible to metabolic drug–drug interactions with drugs that are moderate or strong CYP3A inhibitors (e.g. ritonavir and erythromycin) or CYP3A inducers (e.g. rifampin and efavirenz); coadministration of these drugs may increase or decrease plasma concentrations of simeprevir, respectively, and should be avoided. Clinical studies have shown that simeprevir is a mild inhibitor of CYP1A2 and intestinal CYP3A but does not inhibit hepatic CYP3A. The effects of simeprevir on these enzymes are of clinical relevance only for narrow-therapeutic-index drugs that are metabolized solely by these enzymes (e.g. oral midazolam). Simeprevir does not have a clinically relevant effect on the pharmacokinetics of rilpivirine, tacrolimus, oral contraceptives and several other drugs metabolized by CYP enzymes. Simeprevir is a substrate and inhibitor of the transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and OATP1B1/3. Cyclosporine is an inhibitor of OATP1B1/3, BCRP and P-gp, and a mild inhibitor of CYP3A; cyclosporine causes a significant increase in simeprevir plasma concentrations, and coadministration is not recommended. Clinical studies have demonstrated increases in coadministered drug concentrations for drugs that are substrates of the OATP1B1/3, BRCP (e.g. rosuvastatin) and P-gp (e.g. digoxin) transporters; these drugs should be administered with dose titration and or/close monitoring.

Key Points

Simeprevir is primarily metabolized by cytochrome P450 (CYP) 3A, and coadministration of drugs that are moderate or strong CYP3A inducers or inhibitors should be avoided.

Simeprevir is a mild intestinal, but not hepatic, CYP3A inhibitor and is an inhibitor and substrate of P-glycoprotein, organic anion transporting polypeptide and breast cancer resistance protein transporters.

Simeprevir can be safely coadministered with a wide variety of drugs.

1 Introduction

Hepatitis C virus (HCV) infection affects an estimated 170 million people worldwide and is a major source of morbidity and mortality [1]. Prior to the approval of direct-acting antiviral agents in 2011, the standard of care was pegylated interferon (PegIFN) and ribavirin (RBV) combination therapy, which induced a sustained virological response (SVR) in ≥80 % of patients with HCV genotypes 2 and 3 but in only ~40–50 % of those with HCV

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genotype 1 [2]. The significantly improved SVR rates observed with direct-acting antiviral agents has led to the substantial evolution of HCV treatment paradigms [3].

Simeprevir is an NS3/4A protease inhibitor approved for the treatment of chronic HCV infection, as a component of combination therapy [4, 5]. The 2014 American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) guidelines now include a recommendation for use of simeprevir, in combination with sofosbuvir (±RBV), for the treatment of HCV genotype 1 infection in treatment-experienced patients and for treatment-naïve patients who are ineligible for interferon (IFN); simeprevir is also recommended as part of several alternative treatment regimens, including those for HCV genotype 4 and HIV co-infection [3].

Simeprevir has demonstrated high SVR rates in patients with HCV genotype 1 infection during phase II and III trials [4–10]. In the phase II COSMOS trial, combination therapy with simeprevir and sofosbuvir (±RBV), an IFN-free regimen, was demonstrated to have an SVR 12 weeks after the planned end of treatment (SVR12) of 92–94 % in treatment-naïve and treatment-experienced subjects (>60 % Caucasian subjects in each study group) [10]. In the phase III QUEST (QUEST-1 and QUEST-2) and PROMISE trials, combination therapy with simeprevir plus PegIFN and RBV demonstrated SVR12 rates of 80 % in treatment-naïve subjects and 79.2 % in prior relapser subjects (>90 % Caucasian subjects) [4, 7, 9, 11]. Simeprevir has also shown efficacy in the treatment of subjects with HCV genotype 1 and HIV co-infection and in subjects with HCV genotype 4 when used in combination with PegIFN and RBV [12, 13].

The safety of simeprevir has also been demonstrated in phase II and III trials [4, 7–10, 14]. In the COSMOS trial, which evaluated simeprevir plus sofosbuvir, <5 % of subjects experienced grade 3–4 adverse events, excluding subjects with increased blood amylase levels (reported in 4–7 % of each study group; no cases of pancreatitis were reported) [10]. In this trial, the most common adverse events were fatigue, headache and nausea. Pooled results from three phase III trials that evaluated simeprevir plus IFN and RBV (QUEST-1, QUEST-2 and PROMISE) demonstrated similar rates of grade 3–4 adverse events with simeprevir plus PegIFN and RBV compared with PegIFN and RBV alone (23 and 25 %, respectively) [4, 7, 9, 11]. Adverse events occurring with ≥3 % frequency with the addition of simeprevir in comparison with PegIFN and RBV alone included rash (photosensitivity), pruritus, nausea, myalgia and dyspnoea. Of note, transient increases in bilirubin were observed in the phase II COSMOS trial and in the phase III QUEST-1, QUEST-2 and PROMISE trials [4, 7, 9, 10]. These were most prominent in the setting of simeprevir and RBV coadministration, and can be explained by the inhibition of organic anion transporting polypeptide (OATP) 1B1 and multidrug resistance-associated protein (MRP) 2 hepatic bilirubin transporters by simeprevir, in combination with elevated bilirubin levels as a result of RBV-associated red blood cell haemolysis [10].

Potential drug–drug interactions among these relatively new direct-acting antiviral agents, or between these agents and other therapies, are important to evaluate because of the possibility of coadministration [15]. This article reviews the clinical pharmacokinetics and drug–drug interaction data on simeprevir.

2 Clinical Pharmacokinetics of Simeprevir

Simeprevir is orally bioavailable, with maximum plasma concentration (C_{max}) values being observed approximately 4–6 h postdose [16]. The area under the concentration-time curve (AUC) was shown to be increased from 61 and 69 % when simeprevir was administered with a high-fat/high-caloric and normal-caloric breakfast, respectively; therefore, it is recommended that simeprevir be administered with food [17].

Simeprevir is extensively bound to plasma proteins (>99.9 %), largely to albumin; binding is not significantly different in renal or hepatic impairment [11, 18, 19]. In vitro data suggest that OATPs, including OATP1B1 and OATP1B3, mediate hepatic uptake of simeprevir [20]. Elimination occurs mainly via biliary excretion [20].

Simeprevir is metabolized by the liver. In vitro studies suggest that metabolism occurs primarily through the CYP enzyme, CYP3A [21]. In addition to being a substrate for CYP3A and OATPs, simeprevir is a substrate for several efflux transporters, including MRP2, P-gp and breast cancer resistance protein (BCRP; on the basis of in vitro studies; data on file) [20].

In clinical studies, the mean terminal elimination half-life was shown to be approximately 10–13 h in subjects without HCV infection and approximately 41 h in HCV-infected subjects [16]. The observed extension of the simeprevir half-life in HCV-infected subjects compared with healthy participants may be due to the presence of HCV infection in combination with the consequences of the underlying liver disease; however, the number of HCV-infected subjects evaluated was relatively small ($n = 6$). Once-daily dosing is recommended for HCV-infected patients [17]; with this regimen, steady state is attained in 7 days [11].

Other pharmacokinetic characteristics of simeprevir include the following: C_{max} and AUC increased more than dose proportionally following administration of repeated doses of simeprevir (doses between 75 mg and 200 mg

daily) [11, 16]. The plasma exposures (C_{max} and AUC) were similar with simeprevir in combination with PegIFN-alfa and RBV in comparison with simeprevir alone [11]. The AUC value was 2–3 times higher in subjects infected with HCV than in uninfected subjects, a phenomenon that has been reported previously with selected protease inhibitors used to treat HIV infection, oral midazolam and other HCV protease inhibitors [22–24]; however, as studies comparing drug pharmacokinetics in HIV-1-infected subjects versus healthy participants have demonstrated, physiological changes that accompany infection can have a variety of effects on individual metabolic enzymes, including those in the same family [23, 25]. Altered pharmacokinetics may result from differences in the numbers of functional hepatocytes, transporter expression and/or CYP expression in HCV-infected individuals compared with individuals without HCV infection. Subclinical liver disease could also potentially contribute to differences in simeprevir pharmacokinetics in HCV-infected individuals compared with healthy controls.

Simeprevir exposure was mildly increased in subjects with severe renal impairment compared with subjects with normal renal function [the AUC from 0 to 24 h (AUC_{24h}) and C_{max} increased 62 and 34 %, respectively] [18]; no dose adjustment is required in patients with severe renal impairment [11]. Simeprevir exposure was also increased by approximately 2-fold in non-HCV-infected subjects with moderate hepatic impairment compared with matched healthy controls; exposure was further increased in non-HCV-infected subjects with severe hepatic dysfunction (approximately a 2-fold increase in exposure in severe compared with moderate hepatic impairment) [19]. As a result, no dose recommendation can be given for patients with moderate or severe hepatic impairment [11].

Simeprevir has a wide therapeutic index, with no clear relationships between plasma exposure and efficacy and safety parameters. In general, there were no consistent relationships between simeprevir exposure and virological response parameters in phase II and III studies at dose ranges between 75 and 150 mg.

3 Drug Interactions Caused by Simeprevir as an Inhibitor or Inducer

In vitro studies suggest that simeprevir is a moderate inhibitor of CYP2A6, CYP2C8 and CYP2D6, and a weak inhibitor of CYP2C19 and CYP3A [11]; therefore, clinical studies were performed to investigate the potential of simeprevir to alter the pharmacokinetics of drugs metabolized by these CYP enzymes. In addition, in vitro studies conducted to assess the cause of transient bilirubin elevations that were observed in clinical trials suggested that simeprevir is also an inhibitor of the transporters OATP1B1, MRP2, bile salt export pump (BSEP), P-gp and BCRP [11, 20]. In vitro studies demonstrated no clinically relevant inhibition of cathepsin A (data on file).

3.1 Metabolic Drug–Drug Interactions

3.1.1 Drugs Metabolized by CYP Enzymes

The effect of simeprevir on the CYP system was clinically evaluated in a phase I, two-period, open-label, randomized, crossover trial, which utilized five representative CYP probes [21]. In this trial, 16 healthy subjects (five male) received oral midazolam (0.075 mg/kg; a probe for intestinal CYP3A) and a drug cocktail consisting of intravenous midazolam (0.025 mg/kg; a probe for hepatic CYP3A), warfarin (10 mg; a probe for CYP2C9), caffeine (150 mg; a probe for CYP1A2), omeprazole (40 mg; a probe for CYP2C19) and dextromethorphan (30 mg; a probe for CYP2D6) alone or in combination with 150 mg of simeprevir under fed conditions. All drugs were administered orally except for midazolam, which was administered both orally (alone) and intravenously (as part of the drug cocktail) to differentiate between intestinal and hepatic CYP3A activity. The presence of simeprevir resulted in increased exposure to oral midazolam (the C_{max} and AUC from time zero to the time of the last measurable concentration (AUC_{last}) increased by 1.31- and 1.45-fold, respectively) and caffeine (the C_{max} and AUC_{last} increased by 1.12- and 1.26-fold, respectively; see Table 1). Simeprevir coadministration also resulted in increased exposure to omeprazole (the C_{max} and AUC_{last} increased by 1.14- and 1.21-fold, respectively), and little to no change in exposure to dextromethorphan (the C_{max} and AUC_{last} increased by 1.21- and 1.08-fold, respectively) and warfarin (the C_{max} and AUC_{last} increased by 1.00- and 1.04-fold, respectively). An increased parent drug to metabolite ratio of 1.31 was seen for oral midazolam, suggesting that the increased midazolam exposure was due to mild intestinal CYP3A inhibition; this increase was not seen for intravenous midazolam, suggesting no effect on CYP3A hepatic metabolism. Additionally, there was a 1.34-fold increase in the parent drug to metabolite ratio of caffeine, suggesting mild CYP1A2 inhibition by simeprevir. The parent compound to metabolite ratios of warfarin, omeprazole and dextromethorphan were similar with and without administration of simeprevir, suggesting no relevant clinical interaction of simeprevir with CYP2C9, CYP2C19 and CYP2D6.

CYP1A2 substrates (e.g. caffeine), CYP2C9 substrates (e.g. warfarin) and CYP2C19 substrates (e.g. omeprazole) may be coadministered with simeprevir without dose adjustments [21]. Exposure of CYP3A substrates may be mildly

Table 1 Effects of simeprevir on the pharmacokinetics (PK) of coadministered probe substrates

Coadministered drug	Cytochrome enzyme probe	C_{max}[a]	AUC_{last}[a]	Parent to metabolite ratio
Midazolam: oral[b]	CYP3A (intestinal)	1.31 (1.19–1.45)	1.45 (1.35–1.57)	1.31 (1.21–1.42)
Midazolam: intravenous[b]	CYP3A (hepatic)	0.78 (0.52–1.17)	1.10 (0.95–1.26)	1.01 (0.86–1.18)
S-warfarin[c]	CYP2C9	1.00 (0.94–1.06)	1.04 (1.00–1.07)	0.98 (0.86–1.12)
Caffeine[d]	CYP1A2	1.12 (1.06–1.19)	1.26 (1.21–1.32)	1.34 (1.26–1.42)
Omeprazole[e]	CYP2C19	1.14 (0.93–1.39)	1.21 (1.00–1.46)	0.98 (0.85–1.12)
Dextromethorphan[f]	CYP2D6	1.21 (0.93–1.57)	1.08 (0.87–1.35)	0.99 (0.80–1.23)

AUC_{last} area under the concentration-time curve from time zero to the time of the last measurable concentration, *CI* confidence interval, *C_{max}* maximum plasma concentration, *CYP* cytochrome P450

[a] The values represent the least squares mean ratio (and 90 % CI) of each PK parameter of the cytochrome probe substrate coadministered with simeprevir versus without simeprevir

[b] The metabolite is 1-OH-midazolam

[c] The metabolite is 7-OH-S-warfarin

[d] The metabolite is paraxanthine

[e] The metabolite is 5-OH-omeprazole

[f] The metabolite is dextrorphan

increased (31 % for oral midazolam) because of inhibition of intestinal CYP3A by simeprevir; therefore, caution should be exercised when simeprevir is coadministered with CYP3A substrates with a narrow therapeutic index.

3.1.1.1 Rilpivirine Rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in the treatment of HIV, is a substrate of CYP3A. In an open-label, randomized, three-period crossover study with a washout period of at least 14 days, 24 healthy subjects (12 male) received simeprevir (150 mg once daily), rilpivirine (25 mg once daily) or simeprevir (150 mg once daily) plus rilpivirine (25 mg once daily) for 10 days under fed conditions [26]. The C_{max} of simeprevir increased by 1.10-fold; the minimum plasma concentration (C_{min}) and AUC_{24h} were unchanged (Table 2). The mean C_{min} of rilpivirine increased by 1.25-fold; the C_{min} and AUC_{24h} were unchanged (Table 3; see also Table 4 for a concise summary of data included in Tables 2 and 3). Neither simeprevir exposure nor rilpivirine exposure was affected to a clinically relevant degree; therefore, no dose adjustment is required for coadministration of these drugs.

3.1.1.2 Ethinylestradiol and Norethindrone Ethinylestradiol and norethindrone are commonly used oral contraceptives. RBV, which can be used in combination therapy with simeprevir, is known to be teratogenic, and effective methods of contraception are required for women of childbearing potential who are taking RBV [27]; therefore, many patients will be receiving oral contraceptive therapy while on simeprevir. The metabolism of ethinylestradiol occurs predominately through CYP3A and CYP2C9 [28]. CYP3A is also involved in the metabolism of norethindrone [29]. Interactions between simeprevir and ethinylestradiol/norethindrone were evaluated in an open-label study of 18 healthy female subjects [30]. Subjects received ethinylestradiol/norethindrone (35 μg/1 mg) for two consecutive 28-day oral contraceptive cycles (21 days of the drug, followed by a 7-day drug-free period). During the second cycle (days 29–56), subjects also received simeprevir (150 mg once daily) for the last 10 days of ethinylestradiol/norethindrone treatment (days 40–49; all treatments were taken under fed conditions). The C_{min} and AUC_{24h} for ethinylestradiol were similar with coadministration of simeprevir in comparison with ethinylestradiol/norethindrone alone [although the 90 % confidence interval (CI) for the AUC_{24h} ratio of test to reference did not include 1]; the C_{max} was 18 % higher with coadministration (Table 3). The C_{max} and AUC_{24h} values for norethindrone were similar with coadministration of simeprevir in comparison with ethinylestradiol/norethindrone alone (although the 90 % CI for the AUC_{24h} ratio of test to reference did not include 1); the C_{min} was 24 % higher with coadministration. These differences are unlikely to be clinically relevant. Serum hormone levels for progesterone, follicle-stimulating hormone and luteinizing hormone were also evaluated in this study; coadministration of simeprevir did not yield differences in these hormone levels in comparison with ethinylestradiol/norethindrone alone. Therefore, ethinylestradiol/norethindrone may be used in combination with simeprevir without dose adjustment.

Table 2 Effects of coadministered drugs on the pharmacokinetics (PK) of simeprevir (multiple dosing)

Coadministered drug	Effect on PK[a]	PK parameters (ratio of simeprevir coadministration to simeprevir alone)[b]		
		C_{max}	AUC_{24h}	C_{min}
Erythromycin	↑	4.53 (3.91–5.25)	7.47 (6.41–8.70)	12.74 (10.19–15.93)
Rifampin	↓	1.31 (1.03–1.66)	0.52 (0.41–0.67)	0.08 (0.06–0.11)
Escitalopram	↓	0.80 (0.71–0.89)	0.75 (0.68–0.83)	0.68 (0.59–0.79)
Ritonavir	↑	4.70 (3.84–5.76)	7.18 (5.63–9.15)	14.35 (10.29–20.01)
Darunavir/ritonavir[c]	↑	1.79 (1.55–2.06)	2.59 (2.15–3.11)	4.58 (3.54–5.92)
Efavirenz	↓	0.49 (0.44–0.54)	0.29 (0.26–0.33)	0.09 (0.08–0.12)
Rilpivirine	↔	1.10 (0.97–1.26)	1.06 (0.94–1.19)	0.96 (0.83–1.11)
Tenofovir	↓	0.85 (0.73–0.99)	0.86 (0.76–0.98)	0.93 (0.78–1.11)
Raltegravir	↔	0.93 (0.85–1.02)	0.89 (0.81–0.98)	0.86 (0.75–0.98)

AUC_{24h} area under the concentration-time curve from 0 to 24 h, *CI* confidence interval, *C_{max}* maximum plasma concentration, *C_{min}* minimum plasma concentration

[a] The arrows signify the effects on the PK of simeprevir according to the change in the mean ratio of the AUC_{24h}: an increase (↑), decrease (↓) or no change (↔; if the 90 % CI is within the range of 0.80–1.25)

[b] The values represent the least squares means (90 % CIs) of coadministered simeprevir compared with simeprevir alone

[c] The dose of simeprevir was 150 mg once daily when it was administered alone, compared with 50 mg when it was coadministered with darunavir/ritonavir

Table 3 Effects of simeprevir on the pharmacokinetics (PK) of coadministered drugs

Coadministered drug	Effect on PK[a]	PK parameters (ratio of simeprevir coadministration to administration alone)[b]		
		C_{max}	AUC_{24h}	C_{min}
Erythromycin	↑	1.59 (1.23–2.05)	1.90 (1.53–2.36)	3.08 (2.54–3.73)
Rifampin	↔	0.92 (0.80–1.07)	1.00 (0.93–1.08)	NA
Escitalopram	↔	1.03 (0.99–1.07)	1.00 (0.97–1.03)	1.00 (0.95–1.05)
Ethinylestradiol	↔	1.18 (1.09–1.27)	1.12 (1.05–1.20)	1.00 (0.89–1.13)
Norethindrone	↔	1.06 (0.99–1.14)	1.15 (1.08–1.22)	1.24 (1.13–1.35)
Atorvastatin	↑	1.70 (1.42–2.04)	2.12 (1.72–2.62)	NA
Simvastatin	↑	1.46 (1.17–1.82)	1.51 (1.32–1.73)	NA
Rosuvastatin	↑	3.17 (2.57–3.91)	2.81 (2.34–3.37)	NA
Digoxin	↑	1.31 (1.14–1.51)	1.39 (1.16–1.67)	NA
Cyclosporine	↑	1.16 (1.07–1.26)	1.19 (1.13–1.26)	NA
Tacrolimus	↓	0.76 (0.65–0.90)	0.83 (0.59–1.16)	NA
Methadone	↔	1.03 (0.97–1.09)	0.99 (0.91–1.09)	1.02 (0.93–1.12)
Ritonavir	↑	1.23 (1.14–1.32)	1.32 (1.25–1.40)	1.44 (1.30–1.61)
Darunavir	↑	1.04 (0.99–1.10)	1.18 (1.11–1.25)	1.31 (1.13–1.52)
Efavirenz	↔	0.97 (0.89–1.06)	0.90 (0.85–0.95)	0.87 (0.81–0.93)
Rilpivirine	↔	1.04 (0.95–1.13)	1.12 (1.05–1.19)	1.25 (1.16–1.35)
Tenofovir	↔	1.19 (1.10–1.30)	1.18 (1.13–1.24)	1.24 (1.15–1.33)
Raltegravir	↑	1.03 (0.78–1.36)	1.08 (0.85–1.38)	1.14 (0.97–1.36)

AUC_{24h} area under the concentration-time curve from 0 to 24 h, *CI* confidence interval, C_{max} maximum plasma concentration, C_{min} minimum plasma concentration, *NA* not available

[a] The arrows signify the effects on the PK of the coadministered drug according to the change in the mean ratio of the AUC_{24h}: an increase (↑), decrease (↓) or no change (↔; if the 90 % CI is within the range of 0.80–1.25)

[b] The values represent the least squares means (90 % CIs) of coadministration with simeprevir in comparison with the coadministered drug used alone

Table 4 Summary of the effects of coadministration on the pharmacokinetics (PK) of simeprevir and coadministered drugs[a]

Coadministered drug	Effect on simeprevir PK[b]	Effect on coadministered drug PK[b]	Clinical comment
Erythromycin	↑	↑	Coadministration not recommended
Rifampin	↓	↔	Coadministration not recommended
Escitalopram	↓	↔	No dose adjustments needed for either drug
Ritonavir	↑	↑	Coadministration not recommended
Darunavir	NA	↑	No comment
Darunavir/ritonavir[c]	↑	NA	Coadministration not recommended
Efavirenz	↓	↔	Coadministration not recommended
Rilpivirine	↔	↔	No dose adjustments needed for either drug
Tenofovir	↓	↔	No dose adjustments needed for either drug
Raltegravir	↔	↑	No dose adjustments needed for either drug
Atorvastatin	↔	↑	Use the lowest necessary dose of atorvastatin, but do not exceed a daily dose of 40 mg when it is coadministered with simeprevir
Simvastatin	↔	↑	Titrate the simvastatin dose carefully and use the lowest necessary dose of it while monitoring for safety when it is coadministered with simeprevir

AUC_{24h} area under the concentration-time curve from 0 to 24 h, *CI* confidence interval, *NA* not applicable

[a] Summary of data contained in Tables 2 and 3

[b] The arrows signify the effects on the PK of the indicated drug according to the change in the mean ratio of the AUC_{24h}: an increase (↑), decrease (↓) or no change (↔; if the 90 % CI is within the range of 0.80–1.25)

[c] The dose of simeprevir was 150 mg once daily when it was administered alone, compared with 50 mg when it was coadministered with darunavir/ritonavir

3.1.1.3 Cyclosporine/Tacrolimus Cyclosporine and tacrolimus are both immunosuppressants used to prolong allogeneic transplant survival, including liver transplants [31]. Both are substrates for and mild inhibitors of CYP3A, and are substrates for P-gp. Cyclosporine is also an inhibitor of P-gp, OATP1B1 and OATP1B3 [31]. Drug–drug interactions between simeprevir and cyclosporine or tacrolimus are important, as coadministration may occur in patients with HCV in the setting of liver transplantation. In a two-panel, randomized, open-label, two-period crossover study, 14 healthy subjects (eight male) received cyclosporine (100 mg single dose) or simeprevir (150 mg once daily on days 1–10) plus cyclosporine (100 mg single dose on day 7), and 14 healthy subjects (seven male) received tacrolimus (2 mg single dose) or simeprevir (150 mg once daily on days 1–12) plus tacrolimus (2 mg single dose on day 7) [32]. Simeprevir alone was administered under fed conditions; all other treatments were administered under fasting conditions. For cyclosporine, the mean C_{max} was increased by 1.16-fold and the AUC_{last} was increased by 1.19-fold with simeprevir coadministration in comparison with cyclosporine alone (Table 3). For tacrolimus, the mean C_{max} was decreased by 24 % and the mean AUC_{last} was decreased by 17 % with simeprevir coadministration in comparison with tacrolimus alone. The study was not designed to investigate the effect of immunosuppressants on simeprevir. Preliminary data on the effect of immunosuppressants on simeprevir are available from an ongoing phase II study (see Sect. 4.4).

3.1.1.4 Escitalopram Escitalopram is a selective serotonin reuptake inhibitor used to treat depression. Patients receiving PegIFN-based treatment for HCV experience high rates of depression [33]; therefore, antidepressants are often used in this patient population. Escitalopram is metabolized by CYP3A, CYP2D6 and CYP2C19 [34]. Drug–drug interactions between escitalopram and simeprevir were evaluated in 20 healthy male subjects in a randomized, open-label, three-period crossover study with washout periods of at least 10 days between study periods [35]. Subjects received simeprevir (150 mg once daily), escitalopram (10 mg once daily) or simeprevir (150 mg once daily) plus escitalopram (10 mg once daily) for 7 days; all treatments were given under fed conditions [11]. Pharmacokinetic parameters for escitalopram were unchanged with coadministration in comparison with escitalopram alone (Table 3). Overall, the decrease in simeprevir exposure seen with escitalopram exposure is not clinically relevant, and these medications can be administered concomitantly without dose adjustment.

3.1.1.5 Methadone Methadone is a synthetic narcotic analgesic used to treat opioid dependence. Because intravenous drug use is a common mode of transmission of HCV infection [36], patients with HCV may receive maintenance methadone therapy. Methadone exists as a racemic mixture of R(−) and S(+) enantiomers, with R(−) responsible for most of the therapeutic effect [37]. The metabolism of methadone is not completely understood; however, CYP enzymes (including CYP3A and CYP2D6) likely contribute to it [38]. In an open-label study, 12 HCV-negative, opioid-dependent subjects (ten male) receiving stable methadone maintenance therapy (between 30 and 150 mg once daily) received simeprevir 150 mg once daily for 7 days [39]. Simeprevir exposure alone could not be measured in this study for comparison. However, the C_{max} and AUC_{24h} of simeprevir with coadministration of methadone for 7 days (966 ng/mL and 12,110 ng·h/mL, respectively) were lower than the mean C_{max} and AUC_{24h} reported in a pooled analysis of phase I data in which simeprevir 150 mg was administered alone once daily for 7 days (1992 and 22,850 ng/mL); the difference in simeprevir exposure was not considered clinically relevant. The C_{min}, C_{max} and AUC_{24h} of both methadone enantiomers were unchanged with coadministration of simeprevir in comparison with methadone alone (Table 3). Simeprevir and methadone may be administered simultaneously without dose adjustment.

3.1.1.6 Daclatasvir Daclatasvir, an NS5A replication complex inhibitor, was developed for the treatment of chronic HCV infection (approved in Europe) [40]. It is a CYP3A substrate and an inhibitor of P-gp, OATP1B1 and BCRP [40]. Drug–drug interactions with simeprevir were evaluated in a two-panel, randomized, open-label, two-period crossover study with a washout period of 7 days between study periods. Nineteen healthy subjects (18 male) received daclatasvir (60 mg once daily) or daclatasvir (60 mg once daily) plus simeprevir (150 mg once daily) for 7 days, and 25 healthy subjects (20 male) received simeprevir (150 mg once daily) or simeprevir (150 mg once daily) plus daclatasvir (60 mg once daily) for 7 days; all treatments were administered under fed conditions (data on file). The mean C_{max} and AUC_{24h} of daclatasvir were increased by 1.50- and 1.96-fold, respectively, with coadministration in comparison with daclatasvir alone. The mean C_{max} and AUC_{24h} of simeprevir were increased by 1.39- and 1.44-fold, respectively. No dose adjustment of daclatasvir or simeprevir is required [40].

3.1.2 Drugs Metabolized by Glucuronidation

3.1.2.1 Raltegravir Raltegravir, an HIV integrase inhibitor, which is cleared via glucuronidation using uridine diphosphate glucuronosyltransferase (UGT) 1A1, is indicated for the treatment of HIV infection. Drug–drug interactions were evaluated in a randomized, open-label, three-period crossover study with a washout period of at least 14 days [41]. Twenty-four healthy subjects (17 male) received simeprevir (150 mg once daily), raltegravir (400 mg twice daily) or simeprevir (150 mg once daily) plus raltegravir (400 mg twice daily) for 7 days under fed conditions. Coadministration resulted in no clinically relevant difference in simeprevir or raltegravir exposure (although the 90 % CI for the AUC_{24h} ratio of test to reference for simeprevir did not include 1; see Tables 2 and 3). Simeprevir and raltegravir can be coadministered without dose adjustment.

3.2 Transporter Interactions

3.2.1 Sofosbuvir

Sofosbuvir, an HCV nucleotide analogue NS5B polymerase inhibitor, is indicated for the treatment of HCV infection [22]. Sofosbuvir is a substrate for CatA and carboxylesterase (CES) 1; these enzymes aid in the rapid conversion of >90 % of sofosbuvir to its active metabolite GS-331007 [42]. Sofosbuvir (the parent compound) is also a substrate of BCRP and P-gp. Drug–drug interactions with simeprevir were evaluated in a phase II, randomized, open-label study (the COSMOS study) of HCV treatment-experienced and treatment-naïve subjects (data on file). Subjects received simeprevir (150 mg once daily under fed conditions) and sofosbuvir (400 mg once daily) alone or in combination with RBV. An analysis of serial pharmacokinetic samples obtained from 22 subjects (10 male) demonstrated no clinically significant effect of sofosbuvir on simeprevir exposure. In comparison with another study in which sofosbuvir was administered in the absence of simeprevir, the sofosbuvir C_{max} and AUC_{24h} were increased by 1.19- and 3.16-fold, respectively; the C_{max} of the major metabolite of sofosbuvir, GS-331007, was decreased 31 %, and the AUC_{24h} was unaffected. The increases in sofosbuvir exposure were not considered clinically relevant because of the low transient exposure to this form of the drug relative to the total drug-related material. Simeprevir and sofosbuvir may be coadministered without dose adjustment.

4 Simeprevir as a Substrate of Metabolic Drug–Drug Interactions

Given that simeprevir is primarily metabolized by CYP3A, drugs that induce or inhibit the CYP3A enzyme may decrease or increase simeprevir exposure, respectively.

4.1 CYP3A Inhibitors

4.1.1 Ritonavir

Ritonavir, a protease inhibitor used to treat HIV infection, is a strong CYP3A inhibitor and an inhibitor of P-gp and MRP2 [43]. In a phase I, randomized, open-label, two-period study with a washout period of at least 7 days, 12 healthy male subjects were administered simeprevir (200 mg once daily on days 1–7) or ritonavir (100 mg twice daily on days 1–15) plus simeprevir (200 mg once daily on days 6–12) under fed conditions [21]. Simeprevir exposure was increased after the first dose in the coadministration group, with increases in the C_{max} and AUC_{24h} of 1.30- and 1.83-fold, respectively, in comparison with simeprevir alone. Simeprevir exposure was further increased in subjects who received multiple doses of simeprevir and ritonavir, with increases in the C_{max}, AUC_{24h} and C_{min} of 4.70-, 7.18- and 14.35-fold, respectively, in comparison with administration of simeprevir alone. Given the increase in simeprevir exposure, coadministration of simeprevir with ritonavir is not recommended [11].

4.1.2 Darunavir/Ritonavir

The combination of darunavir, a protease inhibitor, with low-dose ritonavir is used to treat HIV infection [43, 44]. Interactions between darunavir/ritonavir and simeprevir were evaluated in a phase I, randomized, open-label, three-period crossover study with a washout period of at least 7 days [41]. Healthy subjects [$n = 25$ (13 male)] received simeprevir (150 mg once daily), darunavir/ritonavir (800/100 mg once daily) or simeprevir (50 mg once daily) plus darunavir/ritonavir (800/100 mg once daily) for 7 days [41]. A lower dose of simeprevir (50 mg once daily) was used in the simeprevir/darunavir/ritonavir coadministration group because of the increased simeprevir exposure seen with coadministration of simeprevir and ritonavir alone [21]. There was increased exposure to simeprevir with coadministration in spite of the dose-reduction of simeprevir to 50 mg. The C_{max} and AUC_{24h} were 1.79- and 2.59-fold higher, respectively, in comparison with administration of 150 mg simeprevir alone (Table 2) [41]. For darunavir, the C_{max} and AUC_{24h} were unaffected by coadministration (the C_{min} was increased by 1.31-fold; however, the 90 % CIs for the darunavir C_{min} and AUC_{24h} did not include 1; Table 3). For ritonavir, the C_{max} and AUC_{24h} were increased by 1.23- and 1.32-fold, respectively, with coadministration in comparison with ritonavir alone. Given the significant increase in simeprevir exposure, despite dose adjustment, coadministration of simeprevir and darunavir/ritonavir is not recommended.

4.1.3 Erythromycin

The macrolide antibiotic erythromycin is both a moderate CYP3A inhibitor and a P-gp inhibitor [43]. In a phase I, randomized, open-label, three-period crossover study with a washout period of at least 10 days, 24 healthy subjects (eight male) were administered simeprevir (150 mg once daily on days 1–7), erythromycin (500 mg three times daily on days 1–6; 500 mg single dose on day 7) or simeprevir (150 mg once daily on days 1–7) plus erythromycin (500 mg three times daily on days 1–7) under fed conditions [11, 45]. For simeprevir, coadministration with erythromycin increased the mean AUC_{24h}, C_{max} and C_{min} by 7.47-, 4.53- and 12.74-fold, respectively, in comparison with simeprevir alone (Table 2). For erythromycin, coadministration with simeprevir increased the mean AUC from 0 to 8 h (AUC_{8h}) by 1.90-fold and increased the C_{max} and C_{min} by 1.59- and 3.08-fold, respectively, in comparison with administration of erythromycin alone (Table 3). Given the increased exposure to both drugs, coadministration of simeprevir and erythromycin is not recommended.

4.2 CYP3A Inducers

4.2.1 Rifampin

Rifampin is an antituberculosis agent used to treat infections with *Mycobacterium tuberculosis*. It is a CYP3A and P-gp inducer and an inhibitor of OATP1B [46, 47]. Drug–drug interactions with simeprevir were evaluated in a phase I, randomized, open-label, three-period crossover study with a washout period of at least 10 days [21]. Healthy subjects ($n = 21$; 20 male and one female) received simeprevir (200 mg once daily), rifampin (600 mg once daily) or simeprevir (200 mg once daily) plus rifampin (600 mg once daily; when coadministered, they were given in a fasting state) for 7 days [11]. For simeprevir, coadministration decreased the mean C_{min} and AUC_{24h} by 92 and 48 %, respectively, and increased the C_{max} by 1.31-fold in comparison with simeprevir alone; the increase in the C_{max} was likely due to OATP1B inhibition (Table 2). Coadministration did not affect rifampin exposure (Table 3). Simeprevir and rifampin should not be coadministered, as the resultant decrease in simeprevir exposure may result in reduced therapeutic effect of simeprevir.

4.2.2 Efavirenz

Efavirenz, an NNRTI used in the treatment of HIV infection, is a CYP3A and CYP2B6 inducer and an MRP2 inhibitor (MRP2 inhibition based on in vitro data) [48, 49]. Interactions between simeprevir and efavirenz were

evaluated in a phase I, open-label, randomized, three-period crossover study with a washout period of at least 14 days [41]. Twenty-four healthy subjects (13 male) received simeprevir (150 mg once daily), efavirenz (600 mg once daily) or simeprevir (150 mg once daily) plus efavirenz (600 mg once daily) for 14 days; efavirenz was given 2 h postprandially. For simeprevir, coadministration resulted in a 71 % decrease in exposure (the AUC) in comparison with simeprevir alone (Table 2). There was no change in efavirenz exposure with coadministration (Table 3). Coadministration of simeprevir and efavirenz is not recommended, as it may result in a reduced therapeutic effect of simeprevir.

4.3 Transporter Interactions

Simeprevir is a substrate of the hepatic uptake transporter OATP and of several efflux transporters, including MRP2, P-gp and BRCP. Drugs that inhibit the OATP, P-gp, MRP2 or BRCP transporters may affect the pharmacokinetics of simeprevir.

In vitro studies also suggest that simeprevir is an inhibitor of the transporters OATP1B1, OATP1B3, P-gp, MRP2 and BCRP; it has the potential to alter the pharmacokinetics of drugs that are substrates for these transporters (data on file) [11, 20]. It is also an in vitro inhibitor of the bile salt transporters BSEP and sodium taurocholate cotransporting polypeptide (NTCP; data on file).

4.3.1 Digoxin

Digoxin, a P-gp substrate, is a cardiac glycoside used in the treatment of mild to moderate heart failure [43]. In a randomized, open-label, two-period crossover study with a washout period of at least 14 days, 16 healthy subjects (13 male) received digoxin (0.25 mg single dose) or simeprevir (150 mg once daily for 7 days) plus digoxin (0.25 mg single dose on day 7) under fed conditions (data on file) [50]. When digoxin and simeprevir were coadministered, the mean C_{max} and AUC_{24h} of digoxin were increased by 1.31- and 1.39-fold, respectively, in comparison with administration of digoxin alone (Table 3) [11, 50]. Given these results, concentrations of digoxin should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

4.3.2 Tenofovir Disoproxil Fumarate

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor (NtRTI) indicated for the treatment of HIV infection. TDF is taken up by human organic anion transporter (hOAT) 1 and 3 and MRP4, and is an inhibitor of MRP2 [49]. TDF interactions with simeprevir were evaluated in a randomized, open-label, three-period crossover trial with a washout period of at least 14 days. Healthy subjects [$n = 24$ (12 male)] received simeprevir (150 mg once daily), TDF (300 mg once daily) or simeprevir (150 mg once daily) plus TDF (300 mg once daily) for 7 days [41]. In this study, there was no clinically significant decrease in simeprevir exposure with coadministration (the AUC_{24h} decreased 15 %; Table 2). Tenofovir exposure was not affected to a relevant degree (the AUC_{24h} increased by 1.18-fold) with coadministration (Table 3). These results suggest that TDF may be administered with simeprevir without dose adjustment.

4.3.3 Rosuvastatin

Rosuvastatin is a hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, which is not metabolized by CYP enzymes; it is a substrate for OATP1B1, OATP1B3, NTCP and BCRP [51]. Interactions between rosuvastatin and simeprevir were evaluated in 16 healthy subjects (10 male) in a randomized, open-label, two-period crossover study with a washout period of at least 14 days (data on file) [50]. Subjects received rosuvastatin alone (10 mg single dose) or simeprevir (150 mg once daily on days 1–7) plus rosuvastatin (10 mg single dose on day 7) under fed conditions. With simeprevir coadministration, the mean C_{max} and AUC_{24h} of rosuvastatin were increased by 3.17- and 2.81-fold, respectively, in comparison with administration of rosuvastatin alone (Table 3). Like the other statin drugs, rosuvastatin should be titrated to the lowest possible dose, with close safety monitoring when it is used in combination with simeprevir.

4.4 Combined Metabolic and Transporter Interactions

4.4.1 Atorvastatin and Simvastatin

Atorvastatin and simvastatin are HMG-CoA reductase inhibitors indicated for cholesterol blood abnormalities, in conjunction with diet [51, 52]. They are both metabolized by CYP3A and are substrates of OATP1B. In a randomized, open-label, two-panel study, 36 healthy subjects (26 male) received atorvastatin (40 mg single doses on days 1 and 13) plus simeprevir (150 mg once daily on days 4–15) or simvastatin (40 mg single doses on days 1 and 13) plus simeprevir (150 mg once daily on days 4–15) under fed conditions (data on file). There were no clinically relevant changes in the pharmacokinetics of simeprevir with coadministration of either atorvastatin or simvastatin (Table 2). However, the C_{max} and the AUC from time zero to infinity (AUC_{∞}) of atorvastatin were increased by 1.70- and 2.12-fold, respectively, with coadministration in comparison

with atorvastatin administered alone (Table 3) [11]. The C_{max} and AUC_{∞} of simvastatin were also increased with coadministration (by 1.46- and 1.51-fold, respectively) in comparison with simvastatin alone; the C_{max} and AUC_{∞} of its active metabolite, simvastatin acid, were increased by 3.03- and 1.88-fold, respectively (Table 3). Given the increase in atorvastatin and simvastatin exposure with simeprevir coadministration, titration of the dose of atorvastatin or simvastatin to the lowest possible dose, with close monitoring, is recommended.

4.4.2 Cyclosporine and Tacrolimus

Cyclosporine is an inhibitor of OATP, P-gp and CYP3A; mechanistically, an interaction between simeprevir and cyclosporine may be expected (tacrolimus was also evaluated in this study; the results are also presented below) [31]. This is being investigated in an ongoing phase IIa, open-label, multicentre study in subjects with recurrent HCV genotype 1b infection following orthotopic liver transplantation with METAVIR fibrosis scores of F1–F2, who were on stable immunosuppressive therapy with cyclosporine [$n = 9$ (five male)] or tacrolimus [$n = 11$ (eight male)] and received simeprevir (150 mg once daily), daclatasvir (60 mg once daily) or body weight–based RBV (range 1000–1200 mg daily). A planned review of interim pharmacokinetic data (from the day 14 pharmacokinetic analysis) showed increases of 4.7- and 5.8-fold in the C_{max} and AUC_{24h}, respectively, for simeprevir [C_{max} 15,321 ng/mL ($n = 9$); AUC_{24h} 262,618 ng·h/mL] in subjects with F1–F2 fibrosis who were receiving cyclosporine, in comparison with historical data on simeprevir in the absence of cyclosporine (C_{max} 3235 ng/mL; AUC_{24h} 45,202 ng·h/mL; data on file). Therefore, coadministration of simeprevir with cyclosporine is not recommended. This interim analysis demonstrated 79 and 85 % increases in the C_{max} and AUC_{24h} (C_{max} 5780 ng/mL; AUC_{24h} 83,808 ng·h/mL), respectively, of simeprevir in subjects receiving simeprevir plus tacrolimus, in comparison with historical data on simeprevir alone (data on file). These increases are not considered clinically significant, and simeprevir and tacrolimus may be coadministered [11].

5 Theoretical Interactions with Commonly Coadministered Drugs

On the basis of the mechanisms of drug–drug interactions described previously, no interactions would be expected with a number of diabetes medications (metformin, glyburide, glitazones, canagliflozin, insulin), antihypertensives (diuretics, beta-blockers, angiotensin receptor blockers), cardiovascular medications (nitrates, aspirin, clopidogrel, rivaroxaban), antipsychotics or HIV medications (dolutegravir) [50].

6 Conclusions

Simeprevir is metabolized by the CYP system, largely by hepatic CYP3A. Therefore, moderate and strong CYP3A inhibitors, such as ritonavir and erythromycin, may increase plasma concentrations of simeprevir; thus, coadministration is not recommended. Additionally, moderate to strong CYP3A inducers, such as efavirenz, may result in reduced levels of simeprevir and therefore decreased efficacy; thus, coadministration is not recommended. Simeprevir is also a substrate of the OATP, MRP2, P-gp and BCRP transporters. Cyclosporine is an inhibitor of OATP1B1/3, BCRP and P-gp, and is a mild inhibitor of CYP3A, which causes a significant increase in simeprevir exposure with coadministration; thus, coadministration is not recommended.

Simeprevir has mild inhibitory effects on the CYP metabolic enzymes, including mild inhibition of intestinal CYP3A and CYP1A2. This was demonstrated by mild increases in the exposure to oral midazolam (31 %) and caffeine (12 %) with coadministration of simeprevir, in comparison with administration of midazolam and caffeine alone. Simeprevir does not have a clinically relevant effect on several other drugs metabolized by CYP enzymes, including tacrolimus.

Simeprevir is an inhibitor of the efflux transporter P-gp, resulting in an increase in digoxin concentrations when these drugs are coadministered. Simeprevir is also an inhibitor of the hepatic uptake transporters OATP1B1/3 and BCRP, which results in increased exposure to rosuvastatin, atorvastatin and simvastatin. Therefore, drugs such as statins (atorvastatin, simvastatin, rosuvastatin) and digoxin may be administered with dose titration and or/close monitoring.

Studies have demonstrated that simeprevir can be used safely and effectively, without dose adjustment, with a wide variety of medications, such as the NNRTI rilpivirine, NtRTIs (TDF), integrase inhibitors (raltegravir), oral contraceptives (ethinylestradiol, norethindrone), omeprazole, dextromethorphan and escitalopram.

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Compliance with Ethical Standards

Disclosures The authors have had full control of all primary data and have agreed to allow the journal to review these data if requested.

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