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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Tolerability of Anti-Hepatitis C Virus Treatment with Ombitasvir, Paritaprevir, Ritonavir, with or Without Dasabuvir, in Subjects with Renal Impairment

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Abstract

Background The direct-acting antiviral agent (DAA) combination of ombitasvir and paritaprevir (administered with ritonavir) with (3D regimen) or without (2D regimen) dasabuvir has shown very high efficacy rates in the treatment of chronic hepatitis C virus (HCV) infection. Renal impairment, a common comorbidity in patients with chronic HCV infection, can influence the pharmacokinetics of antiviral agents and hence their efficacy and safety profiles.

Objective The aim of this study was to evaluate the influence of renal impairment on the pharmacokinetics and tolerability of the 3D and 2D regimens.

Methods Overall, 24 subjects, six in each of four renal function groups (normal, mild, moderate, and severe), received a single dose of the 3D and 2D regimens in separate dosing periods. Plasma and urine were analyzed to assess the effect of renal impairment on drug exposure.

Results DAA exposures changed by up to 21, 37, and 50 % in subjects with mild, moderate, and severe renal impairment, respectively, versus subjects with normal renal function. Ritonavir exposure increased with the degree of renal impairment (maximum 114 %). The half-lives of DAAs and ritonavir in subjects with renal impairment were generally comparable with those in healthy subjects. No safety or tolerability concerns arose in this study.

Conclusion The 3D and 2D regimens do not require dose adjustment for patients with HCV infection and concomitant renal impairment.

Key Points

The pharmacokinetics of two direct-acting antiviral agent (DAA) regimens (i.e. the 3D and 2D regimens) that have been approved for the treatment of hepatitis C virus (HCV) infection were assessed in subjects with varying degrees of renal impairment.

The presence of renal impairment increased DAA exposures to a limited extent. Ritonavir exposure increased with the degree of renal impairment (maximum 114 %).

This single-dose study in patients without HCV suggests that the 3D and 2D regimens may be viable treatment options for patients with HCV and impaired renal function.

1 Introduction

An estimated 7.8 % of patients with end-stage renal disease have comorbid chronic hepatitis C virus (HCV) infection [1]. Moreover, epidemiologic studies indicate that chronic

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HCV infection is an independent risk factor for developing chronic renal insufficiency [2–4]. In a large, retrospective cohort, significantly more patients with HCV infection and no renal impairment at baseline developed stage 3–5 chronic kidney disease (CKD) within 6 years compared with patients without HCV ($p < 0.0001$) [3]. In addition, a Kaplan–Meier survival analysis indicated that the time to development of CKD was appreciably shorter in HCV-infected participants than in participants without HCV [3].

Treating HCV in patients with renal impairment is challenging due to the potential for increases in drug exposure, an issue that manifests with certain direct-acting antiviral (DAA) and interferon-based regimens [5, 6]. A novel, interferon-free combination of three DAA agents (i.e. the 3D regimen; ombitasvir/paritaprevir/ritonavir plus dasabuvir) with and without ribavirin has recently been added to the HCV treatment armamentarium. The drugs that compose the 3D regimen have unique mechanisms of action. Ombitasvir is a novel non-structural protein 5A inhibitor, paritaprevir (identified as a lead compound by AbbVie Inc. and Enanta Pharmaceuticals) is a potent non-structural protein 3/4A protease inhibitor, and dasabuvir is a non-nucleoside, non-structural protein 5B polymerase inhibitor. Both ombitasvir and paritaprevir have shown potent antiviral activity in vitro against HCV genotypes (GTs) 1a, 1b, 2a, 3a, and 4a [7, 8]. Paritaprevir is metabolized primarily by cytochrome P450 (CYP) 3A isozymes and is thus co-administered with ritonavir (designated paritaprevir/r), a potent CYP3A4 inhibitor, to enhance drug exposure. In randomized, multicenter, phase III trials, the 3D regimen with ribavirin achieved rates of sustained virologic response 12 weeks post-treatment (SVR_{12}) of 96–100 % in treatment-naïve and treatment-experienced HCV GT1-infected subjects without cirrhosis after 12 weeks of treatment, and 95–100 % after 24 weeks of treatment in subjects with cirrhosis [9–13].

An interferon-free combination of two DAAs—ombitasvir and paritaprevir/r (the 2D regimen) with ribavirin—has recently been approved for the treatment of HCV GT4 infection [14]. In a phase IIb study (PEARL I), the 2D regimen achieved SVR_{12} rates of 100 % with ribavirin and 91 % without ribavirin in a population of treatment-naïve and treatment-experienced patients with HCV GT4 infection [15]. The 2D regimen has also demonstrated efficacy in the treatment of HCV GT1b and GT2 infection [16, 17], and has been approved for the treatment of HCV GT1 infection in Japan.

Because of the frequent occurrence of renal insufficiency in patients with HCV [3], it is essential to determine (i) whether renal function impairment would have an effect on the pharmacokinetics of DAAs administered as a 3D or 2D regimen; (ii) what effect, if any, these changes in pharmacokinetics would have on the safety profiles of the drugs; and (iii) if, consequently, there is a need for dose adjustment of the DAAs in patients with renal insufficiency. Renal clearance is only a minor route of elimination for ombitasvir, paritaprevir, and dasabuvir, with up to 8.8 % of the radiolabeled dose of these DAAs being eliminated renally [18]; hence, increased drug exposure due to impaired renal function is not anticipated. Nevertheless, renal impairment has been associated with alterations in the metabolism of drugs that are not primarily renally excreted, particularly when renal dysfunction is severe [19].

As an initial step toward exploring use of the 3D and 2D regimens in patients with HCV infection and comorbid renal insufficiency, this study evaluated the pharmacokinetics and tolerability of a single dose of the 3D and 2D regimens in subjects without HCV infection who had varying degrees of renal impairment compared with healthy subjects. The results of this study will help provide dosing recommendations for the use of the 3D and 2D regimens in HCV-infected patients with renal impairment.

2 Methods

2.1 Subjects

Men and women (aged 18–70 years) with a body mass index of 18–38 kg/m^2 were eligible for study inclusion. Subjects with normal renal function [creatinine clearance (CrCL) ≥90 mL/min, as measured by the Cockcroft–Gault equation [20]] had to be in generally good health based on medical history, physical examination findings, laboratory profile, and electrocardiographic evidence. Subjects with renal impairment stages 1–4 (CrCL 15–89 mL/min) had to be in stable condition and were assigned to categories of renal impairment as described: mild (CrCL 60–89 mL/min), moderate (CrCL 30–59 mL/min), or severe (CrCL 15–29 mL/min) [19]. Subjects with impaired renal function were enrolled in parallel, whereas subjects with normal renal function were enrolled in a manner that ensured they were matched to subjects with severe renal impairment based on age (±10 years), weight (±10 %), sex, race, and smoking status. Estimated glomerular filtration rate (eGFR) was also determined according to the Modification of Diet in Renal Disease (MDRD) Study equation [21] at study entry; however, values from the MDRD equation were not used to determine subject group assignment. All study participants provided written informed consent.

Subjects were not eligible for study participation if they had tested positive for hepatitis A, B, or C, or were human immunodeficiency virus (HIV) positive. Subjects were also excluded if they had used any medications contraindicated for use with ritonavir, any known strong or moderate

inhibitors or inducers of CYP3A, any inhibitor or inducer of CYP2C8, or any strong inhibitor or inducer of organic anion transporter protein 1B1 and 1B3 within 1 month before study drug administration; had used any creatinine supplement within 2 weeks before screening; or had consumed grapefruit or products containing grapefruit within 72 h before study drug administration.

2.1.1 Study Design and Treatment

This was a phase I, multicenter, single-dose, open-label, two-period study. On the morning of period 1, the 3D regimen was administered as one ombitasvir 25 mg tablet, two paritaprevir/r 75/50 mg tablets, and one dasabuvir 400 mg tablet taken under non-fasting conditions. A washout period of 14 days separated periods 1 and 2. On the morning of period 2, the 2D regimen was administered as one ombitasvir 25 mg tablet and two paritaprevir/r 75/50 mg tablets. Each dose of study drug was taken orally with 240 mL of water approximately 30 min after starting a standardized breakfast. Subjects were confined to the study site and were supervised for approximately 7 days in each period. This study was conducted in accordance with the Good Clinical Practice Guideline as defined by the International Conference on Harmonisation, the Declaration of Helsinki, and all applicable federal and local regulations. The study was approved by independent institutional review boards, and all subjects provided written informed consent.

2.2 Assessments

2.2.1 Pharmacokinetic Assessments

Blood samples for the evaluation of study drug concentrations were collected by venipuncture before dosing (0 h) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24, 30, 36, 48, 72, 96, and 144 h after dosing in each treatment period. In addition, a 10 mL blood sample for determination of plasma protein binding was collected immediately before study drug dosing in period 1. Plasma concentrations of paritaprevir, ritonavir, ombitasvir, dasabuvir, and the M1 metabolite of dasabuvir (dasabuvir M1) were determined using a validated protein precipitation and online solid-phase extraction method with liquid chromatography and tandem mass spectrometric detection [22]. The lower limits of quantitation for paritaprevir, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 were established at 0.590, 4.71, 0.417, 4.39, and 4.58 ng/mL, respectively, using a 100 µL plasma sample.

Urine samples were collected in containers before dosing (0 h) and during the following intervals: 0–12, 12–24, 24–48, 48–72, 72–96, 96–120, and 120–144 h after dosing in both treatment periods. Urine concentrations of paritaprevir, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 were determined using the same general method as that used for the plasma samples. The lower limits of quantitation for paritaprevir, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 were established at 10.1, 10.2, 1.64, 28.6, and 28.3 ng/mL, respectively, using a 100 µL urine sample.

2.2.2 Tolerability

Treatment-emergent adverse events (TEAEs, defined as adverse events reported from the time of study drug administration until 30 days after the last dose of study drug) were assessed continuously throughout the study. Physical examination findings, vital sign measurements, 12-lead electrocardiographic tracings, and clinical laboratory test results were also assessed at baseline (before dosing), and at various times throughout the study.

2.3 Pharmacokinetic and Statistical Analyses

Pharmacokinetic parameters of the DAAs and ritonavir were determined by non-compartmental analysis (SAS version 9.2; SAS Institute Inc., Cary, NC, USA). Pharmacokinetic variables, including the maximum observed plasma concentration (C_{max}), time to C_{max} (peak time, t_{max}), terminal phase elimination half-life ($t_{½}$), area under the plasma concentration–time curve (AUC) from time zero to infinity (AUC_{∞}), and fraction of dose recovered in urine (f_e), were determined. Plasma protein binding of the DAAs and ritonavir was determined at concentrations comparable with their C_{max}.

To determine the impact of renal impairment on the pharmacokinetics of DAAs and ritonavir, regression analyses were conducted for C_{max} and AUC values versus CrCL (estimated using the Cockroft–Gault equation) and eGFR (estimated using the MDRD Study equation) values as measures of renal function, both of which are widely used in clinical practice. Natural-log transformation was used for these pharmacokinetic parameters for the analyses. Separate analyses were conducted for the 3D and 2D regimens. These regression analyses were performed based on recommendations presented in the US FDA and European Medicines Agency guidance documents for evaluation of the effect of renal impairment on the pharmacokinetics of drugs under development [19, 23]. A regression approach is recommended to construct a mathematical model that can successfully predict pharmacokinetic behavior of a drug given information about renal function. Estimated renal function and the pharmacokinetic parameters are treated as continuous variables, which is usually preferred to an analysis in which CrCL

or eGFR values are treated as a categorical variable corresponding to the normal, mild, moderate, and severe renal impairment groups.

The regression models were used to estimate the C_{max} and AUC values for subjects with normal renal function or mild, moderate, or severe renal impairment using the midpoint of the range of CrCL or eGFR values corresponding to different renal impairment categories (e.g. 75, 45, and 22.5 mL/min for subjects with mild, moderate, and severe renal impairment, respectively, and 120 mL/min for subjects with normal renal function). The effect of renal impairment on the pharmacokinetic parameters (C_{max} and AUC) were estimated using the ratios and 90 % confidence intervals for subjects with mild, moderate, or severe renal impairment relative to subjects with normal renal function.

3 Results

3.1 Subjects

A total of 24 subjects (21 men and 3 women) participated in this study, with six subjects in each of the renal function groups (normal, mild, moderate, and severe) (Table 1). All subjects completed the study as planned. The demographic characteristics of participants in the normal renal function and severe renal impairment groups were comparable, consistent with the protocol-designated matching criteria for these two groups. The demographic characteristics of other renal function groups were generally similar, except for the mild renal impairment group, which was the only group to include female participants and was racially homogeneous.

3.2 Pharmacokinetic Assessments

3.2.1 3D Regimen

Drug exposures of 3D regimen components varied with the degree of renal function impairment (Fig. 1; Table 2). Paritaprevir mean AUC values in subjects with mild, moderate, or severe renal impairment were 19, 33, and 45 % higher, respectively, than the mean AUC value for subjects with normal renal function. Ritonavir and dasabuvir AUC values also increased with decreases in renal function, with 42, 80, and 114 % higher ritonavir

Table 1 Demographic and baseline characteristics

Characteristic	Degree of renal impairment			
	Mild [$n = 6$]	Moderate [$n = 6$]	Severe [$n = 6$]	Normal [$n = 6$]
Age, years				
Mean (SD)	68.0 (3.3)	61.8 (5.0)	61.8 (9.5)	59.0 (8.2)
Range	62–71	56–68	47–71	47–69
Race, *n* (%)				
White	6 (100)	4 (67)	5 (83)	5 (83)
Black or African American	0	2 (33)	1 (17)	1 (17)
Sex, *n* (%)				
Male	3 (50)	6 (100)	6 (100)	6 (100)
Female	3 (50)	0	0	0
Weight, kg				
Mean (SD)	69.8 (7.7)	82.7 (11.9)	77.6 (12.1)	91.4 (7.4)
Range	63.1–80.2	68.6–100.5	55.4–89.5	84.0–103.7
BMI, kg/m^2				
Mean (SD)	26.2 (3.1)	28.7 (4.0)	27.2 (3.2)	30.1 (3.1)
Range	22.8–30.3	25.5–36.5	21.1–30.0	25.0–33.1
Tobacco use, *n* (%)				
Former	2 (33)	3 (50)	2 (33)	1 (17)
Never	4 (67)	3 (50)	4 (67)	5 (83)
Alcohol use, *n* (%)				
Former	0	2 (33)	0	0
Current	2 (33)	0	2 (33)	1 (17)
Never	4 (67)	4 (67)	4 (67)	5 (83)
Creatinine clearance (mL/min)				
Mean (range)	69 (63–78)	44 (30–58)	24 (20–29)	121 (100–145)

BMI body mass index, *SD* standard deviation

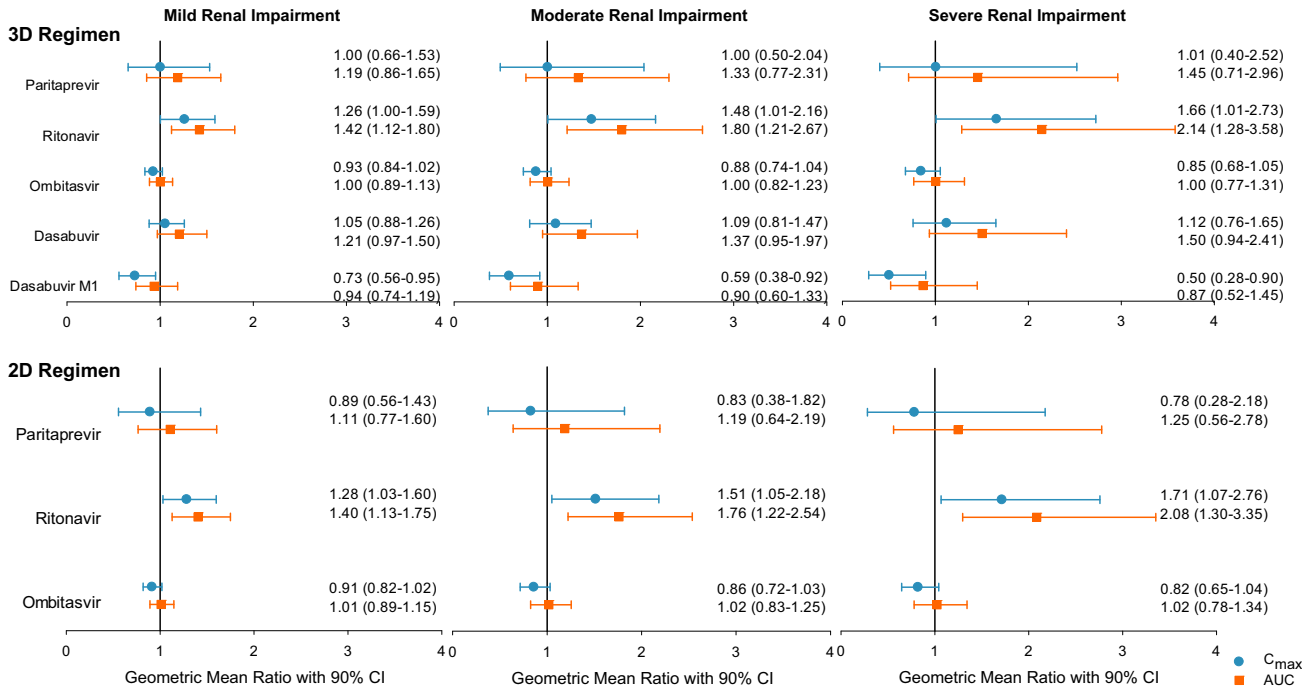

Fig. 1 Ratios and 90 % CIs of C_{max} and AUC for the renal impairment groups relative to the normal renal function group after treatment with the 3D regimen (*top*) or 2D regimen (*bottom*) based on regression analysis. Renal impairment classification was based on creatinine clearance. *CIs* confidence intervals, *AUC* area under the plasma concentration–time curve, C_{max} maximum observed plasma concentration

AUC values and 21, 37, and 50 % higher dasabuvir AUC values in subjects with mild, moderate, or severe renal impairment, respectively, compared with subjects with normal renal function. In contrast, the AUC values for ombitasvir were not affected by renal impairment, and the AUC values of dasabuvir metabolite M1 decreased by 13 % or less when compared with the mean value in subjects with normal renal function.

The changes in C_{max} values in subjects with mild, moderate, and severe renal impairment were, in general, of similar or lower magnitude compared with the changes observed in AUC values. The notable exception was the M1 metabolite of dasabuvir, for which the decreases in C_{max} values were more pronounced compared with changes in AUC values (Fig. 1).

Linear regression analyses using CrCL as the predictor indicated slight increases in paritaprevir and dasabuvir AUC values as renal function decreased (Fig. 2). No such relationship was observed for ombitasvir. A statistically significant correlation between ln(AUC) and CrCL values was observed only for ritonavir ($p < 0.05$). Similar relationships and changes in C_{max} and AUC values were observed when eGFR was used as the predictor instead of CrCL (data not shown).

The half-lives and t_{max} values of the DAAs and ritonavir in subjects with renal impairment were comparable with those in healthy subjects after administration of a single dose of the 3D regimen, with the exception of the $t_{½}$ of dasabuvir, which was prolonged in subjects with renal impairment (Table 2). The urinary fraction of drugs excreted unchanged was ≤1.6 % for all study drugs, regardless of renal function group (Table 2). Paritaprevir, ritonavir, ombitasvir, and dasabuvir were >99 % bound across all renal function groups, and the fraction unbound to plasma proteins was unaffected by renal impairment (data not shown).

3.2.2 2D Regimen

Similar to the results observed with the 3D regimen, drug exposures for the 2D regimen generally varied depending on the degree of renal function impairment (Fig. 1; Table 3). Paritaprevir AUC values for subjects with mild, moderate, and severe renal impairment were 11, 19, and 25 % higher, respectively, compared with AUC values for subjects with normal renal function. Ritonavir drug exposure increased with reduced renal function; subjects with mild, moderate, and severe renal impairment experienced increases in AUC values of 40, 76, and 108 %, respectively, compared with AUC values in subjects with normal renal function. However, regardless of the degree of renal function impairment, AUC values for ombitasvir were minimally affected.

Compared with the changes observed in paritaprevir and ritonavir AUC values discussed above, changes in C_{max}

Table 2 Pharmacokinetics of DAAs and ritonavir after administration of the 3D regimen

Parameter	Degree of renal impairment			
	Mild [$n = 6$]	Moderate [$n = 6$]	Severe [$n = 6$]	Normal [$n = 6$]
Paritaprevir				
C_{max}, ng/mL	780 (465, 1310)	781 (439, 1390)	782 (390, 1570)	778 (391, 1550)
t_{max}, h	5.0 (3.0–8.0)	5.0 (3.0–5.0)	5.0 (4.0–5.0)	5.0 (3.0–6.0)
AUC_{∞}, ng·h/mL	5470 (3680, 8130)	6140 (3900, 9660)	6690 (3850, 11,600)	4610 (2750, 7710)
$t_{½}$, h	5.6 (0.7)	5.9 (3.9)	7.6 (3.2)	6.9 (2.7)
f_e, %	0.21 (0.18)	0.046 (0.062)	0.042 (0.061)	0.035 (0.030)
Ritonavir				
C_{max}, ng/mL	1540 (1160, 2040)	1800 (1320, 2450)	2020 (1390, 2940)	1220 (840, 1770)
t_{max}, h	4.0 (3.0–6.0)	4.5 (3.0–5.0)	5.0 (4.0–5.0)	4.0 (2.0–6.0)
AUC_{∞}, ng·h/mL	10,700 (7880, 14,400)	13,500 (9770, 18,600)	16,100 (11,000, 23,500)	7500 (4990, 11,300)
$t_{½}$, h	5.0 (0.9)	4.1 (1.3)	5.9 (1.6)	4.6 (1.3)
f_e, %	1.6 (0.93)	0.78 (0.39)	0.34 (0.17)	0.48 (0.23)
Ombitasvir				
C_{max}, ng/mL	128 (118, 140)	122 (111, 134)	117 (103, 133)	139 (119, 161)
t_{max}, h	5.0 (4.0–6.0)	5.0 (4.0–6.0)	5.5 (4.0–6.0)	5.0 (4.0–6.0)
AUC_{∞}, ng·h/mL	1940 (1750, 2140)	1940 (1730, 2170)	1940 (1670, 2260)	1930 (1610, 2320)
$t_{½}$, h	47.2 (14.1)	44.5 (8.5)	46.0 (9.6)	38.1 (8.3)
f_e, %	0.025 (0.013)	0.022 (0.014)	0.025 (0.018)	0.023 (0.027)
Dasabuvir				
C_{max}, ng/mL	1690 (1350, 2100)	1740 (1370, 2220)	1790 (1340, 2400)	1600 (1200, 2140)
t_{max}, h	3.5 (2.0–5.0)	4.0 (4.0–5.0)	5.0 (4.0–5.0)	3.5 (2.0–6.0)
AUC_{∞}, ng·h/mL	13,900 (10,700, 18,200)	15,800 (11,700, 21,200)	17,300 (12,100, 24,800)	11,500 (8100, 16,400)
$t_{½}$, h	9.0 (3.3)	10.5 (3.5)	12.0 (5.0)	5.3 (0.7)
f_e, %	0.088 (0.060)	0.055 (0.057)	0.054 (0.060)	0.020 (0.013)
Dasabuvir M1 metabolite				
C_{max}, ng/mL	554 (444, 692)	449 (353, 571)	383 (277, 531)	761 (515, 1130)
t_{max}, h	5.0 (4.0–6.0)	5.0 (5.0–6.0)	5.5 (5.0–6.0)	4.5 (3.0–6.0)
AUC_{∞}, ng·h/mL	5560 (4170, 7430)	5320 (3860, 7340)	5150 (3490, 7600)	5940 (4050, 8720)
$t_{½}$, h	6.2 (0.9)	5.6 (1.1)	7.1 (2.7)	4.9 (0.8)

C_{max} and AUC data are expressed as antilogarithm of least squares mean in log scale (90% confidence interval); estimates are based on regression analysis. t_{max} data are expressed as median and range, and f_e data are expressed as mean (SD). $t_{½}$ data are expressed as harmonic mean (pseudo-SD)

DAA direct-acting antiviral, *3D* ombitasvir/paritaprevir/ritonavir + dasabuvir, C_{max} maximum observed plasma concentration, t_{max} time to C_{max}, AUC_{∞} area under the plasma concentration–time curve from time zero to infinity, $t_{½}$ terminal phase elimination half-life, f_e fraction of drug recovered in urine

values in subjects with mild, moderate, and severe renal impairment were similar or less in magnitude (Fig. 1). Changes in C_{max} values for ombitasvir were greater than those observed for AUC values, but were still modest in all renal impairment groups.

In the linear regression analysis, a statistically significant correlation between ln(AUC) and CrCL values was observed only for ritonavir ($p < 0.05$) (Fig. 2). Similar relationships and changes in C_{max} and AUC values were observed when eGFR was used as a predictor (data not shown).

The half-lives and t_{max} values of the DAAs and ritonavir in subjects with renal impairment were comparable with those in healthy subjects (Table 3). Renal function did not affect the fraction of drugs unbound to plasma proteins, which was <1 % across all renal function groups, nor did it alter the urinary fraction of drugs excreted unchanged, which was ≤1.4 % for all the study drugs (Table 3 and data not shown).

3.3 Tolerability

The majority of TEAEs were judged to be mild or moderate in severity. Reported TEAEs included nausea, diarrhea, vomiting, catheter site erythema/swelling/phlebitis,

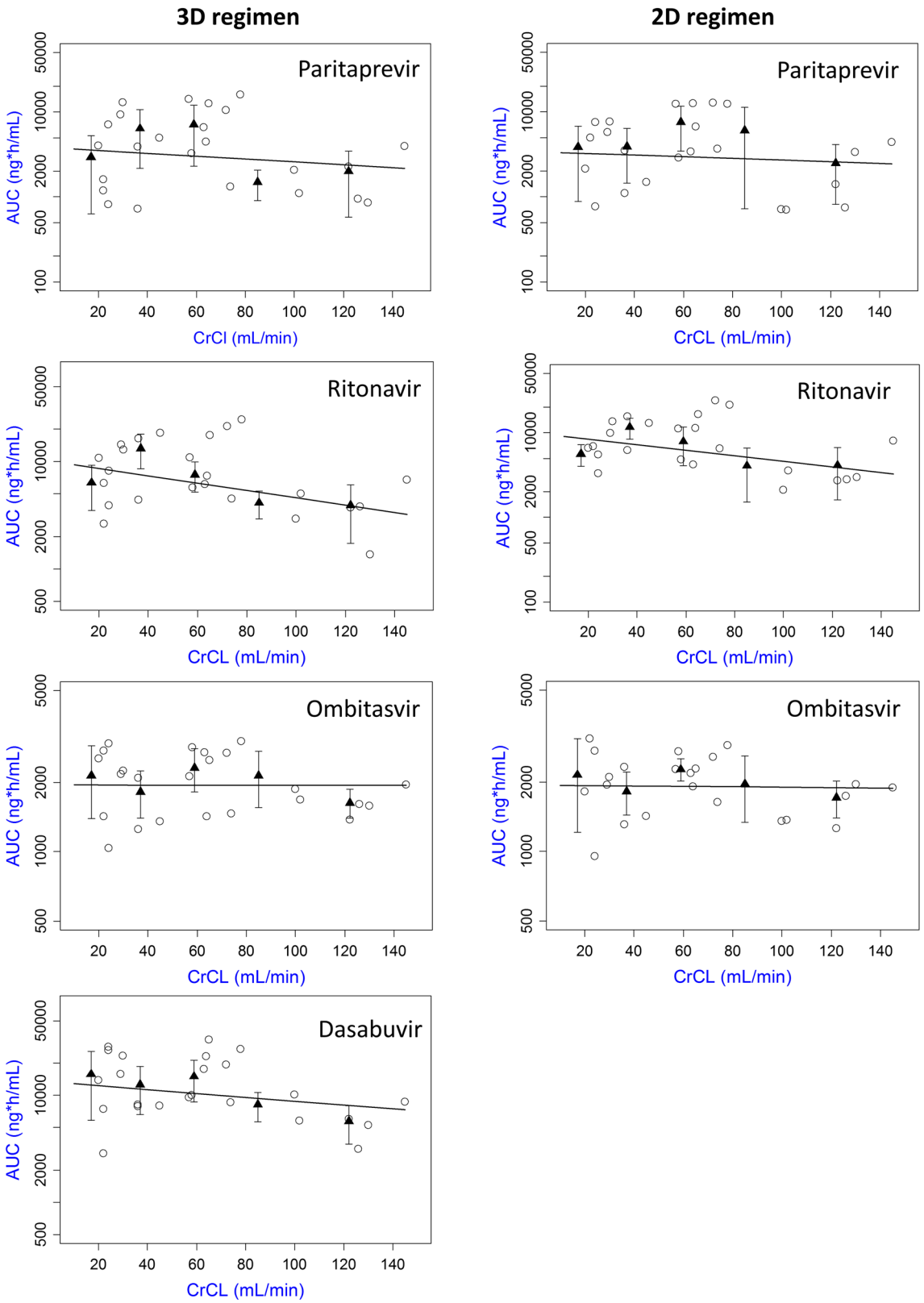

Fig. 2 Linear regression analysis for drug exposure versus renal function after treatment with the 3D or 2D regimen. *Error bars* represent 95 % confidence intervals. *Open circles* represent individual subject values and *closed triangles* represent mean values for bins of four to five subjects. *AUC* area under the plasma concentration–time curve, *CrCL* creatinine clearance

Table 3 Pharmacokinetics of DAAs and ritonavir after administration of the 2D regimen

Parameter	Degree of renal impairment			
	Mild [$n = 6$]	Moderate [$n = 6$]	Severe [$n = 5$][a]	Normal [$n = 6$]
Paritaprevir				
C_{max}, ng/mL	689 (394, 1200)	638 (339, 1200)	603 (279, 1300)	772 (366, 1630)
t_{max}, h	5.0 (3.0–6.0)	5.0 (3.0–5.0)	5.0 (5.0–10.0)	4.0 (2.0–5.0)
AUC_{∞}, ng·h/mL	4530 (2930, 7020)	4850 (2960, 7950)	5110 (2800, 9330)	4100 (2290, 7330)
$t_{½}$, h	6.6 (1.8)	6.6 (2.9)	7.9 (3.0)	6.0 (2.0)
f_e, %	0.13 (0.11)	0.054 (0.082)	0.045 (0.046)	0.016 (0.016)
Ritonavir				
C_{max}, ng/mL	1780 (1360, 2330)	2100 (1550, 2830)	2370 (1650, 3410)	1380 (970, 1980)
t_{max}, h	4.0 (3.0–6.0)	5.0 (3.0–5.0)	5.0 (4.0–6.0)	3.5 (2.0–5.0)
AUC_{∞}, ng·h/mL	10,500 (8000, 13,800)	13,200 (9810, 17,700)	15,600 (11,000, 22,200)	7490 (5170, 10,800)
$t_{½}$, h	4.9 (0.9)	4.4 (2.0)	5.3 (1.7)	5.1 (0.8)
f_e, %	1.4 (0.99)	0.69 (0.32)	0.30 (0.18)	0.41 (0.24)
Ombitasvir				
C_{max}, ng/mL	124 (114, 136)	117 (106, 130)	112 (98, 128)	136 (117, 160)
t_{max}, h	5.0 (5.0–6.0)	5.0 (4.0–6.0)	5.0 (4.0–6.0)	5.0 (3.0–6.0)
AUC_{∞}, ng·h/mL	1900 (1720, 2100)	1910 (1700, 2150)	1920 (1640, 2250)	1880 (1570, 2250)
$t_{½}$, h	45.6 (15.3)	47.0 (11.1)	46.1 (6.1)	40.7 (9.9)
f_e, %	0.027 (0.015)	0.025 (0.029)	0.016 (0.015)	0.023 (0.014)

C_{max} and AUC data are expressed as antilogarithm of least squares mean in log scale (90 % confidence interval); estimates are based on regression analysis. t_{max} data are expressed as median and range, and f_e data are expressed as mean (SD). $t_{½}$ data are expressed as harmonic mean (pseudo-SD)

DAA direct-acting antiviral, *2D* ombitasvir/paritaprevir/ritonavir, C_{max} maximum observed plasma concentration, t_{max} time to C_{max}, AUC_{∞} area under the plasma concentration–time curve from time zero to infinity, $t_{½}$ terminal phase elimination half-life, f_e fraction of drug recovered in urine

[a] One subject was excluded from pharmacokinetic analyses because all 2D regimen study drug levels were below the lower limits of quantitation

myalgia, and concussion. The latter event resulted from a subject accidentally closing a car door on her head 6 days after administration of study treatment in period 2. No TEAEs occurred in more than one subject in any group, and no serious TEAEs were reported. No pattern in the distribution of TEAEs between the renal impairment groups was observed. Laboratory abnormalities were predominantly considered not to be clinically relevant and were deemed related to the subjects' underlying medical conditions. No clinically significant vital sign changes or abnormalities on electrocardiograms were observed during the study.

4 Discussion

This study was designed to characterize the effects of mild, moderate, and severe renal impairment on the pharmacokinetics of paritaprevir, ritonavir, and ombitasvir with and without dasabuvir. The 3D regimen of ombitasvir/paritaprevir/r and dasabuvir is approved for the treatment of chronic HCV GT1 infection in patients with or without cirrhosis in the US, Canada, and the EU. The 2D regimen of ombitasvir/paritaprevir/r is approved for the treatment of chronic HCV GT4 infection in patients without cirrhosis in the US and EU and with compensated cirrhosis in the EU, and for the treatment of HCV GT1 infection in patients without cirrhosis or with compensated cirrhosis in Japan [16].

The results of this study suggest that the pharmacokinetics of the DAAs are not adversely affected by renal impairment. Differences in single-dose drug exposures in the various renal impairment groups versus healthy adults were modest, with DAA exposures altered by 21, 37, and 50 % or less in subjects with mild, moderate, and severe renal impairment, respectively, than in subjects with normal renal function. No significant correlations were observed between DAA exposure and measures of renal function (i.e. CrCL and eGFR values). Pharmacokinetic results were consistent for the 3D and 2D regimens and when either CrCL or eGFR values were used as the measure of renal function.

Increases in exposure based on renal impairment were noted with ritonavir. Mean increases of 42, 80, and

114 % were observed after administration of the 3D regimen in subjects with mild, moderate, and severe renal impairment, respectively, compared with subjects with normal renal function. Similar increases occurred with the 2D regimen administration. Doses of ritonavir up to fourfold higher (400 mg/day) than what is used in the 3D and 2D regimens (100 mg/day) are routinely used for boosting of HIV type 1 protease inhibitors [24]. Ritonavir exposures after administration of the 3D or 2D regimen in subjects with renal impairment would be appreciably lower than those expected with the higher doses of ritonavir used in the context of boosting of HIV protease inhibitors. Dose adjustment is not indicated for ritonavir as part of the 3D or 2D regimen in subjects with renal impairment [14, 18]; however, prescribers should be aware that ritonavir exposures may increase to approximately twofold.

The terminal half-life values of the DAAs and ritonavir were comparable between subjects with renal impairment and those with normal renal function, with the exception of the $t_{½}$ of dasabuvir, which was prolonged in subjects with renal impairment. However, the decline in dasabuvir concentrations up to 48 h post-dosing were comparable in subjects with renal impairment and subjects with normal renal function.

Data from this study suggest that the combination of ombitasvir and paritaprevir/r with or without dasabuvir can be administered without dose adjustment in HCV-infected subjects with mild, moderate, or severe renal impairment. Notably, the 400 mg dose/formulation of dasabuvir used in the current study is bioequivalent with the 250 mg approved dose/formulation. The lack of need for dose adjustment is supported by the minimal-to-moderate observed impact on DAA exposures, and by safety and efficacy data from phase II clinical trials of the 3D regimen in HCV GT1-infected subjects who utilized higher doses of paritaprevir/r (up to 250/100 mg once daily), ombitasvir (up to 200 mg once daily), and dasabuvir (up to 800 mg twice daily) [12, 25, 26]. The safety profiles of the DAAs in these phase II studies were similar to the DAA safety profiles observed in phase III studies, even though DAA exposures at the higher doses used in the phase II studies were expected to provide at least two-fold higher exposures than the doses used in the phase III studies.

Accumulated clinical trial data support that the 3D and 2D regimens are generally well tolerated across a variety of patient populations [9–13, 15, 16]. The lack of a clinically relevant effect on the pharmacokinetics of the DAAs in subjects with mild, moderate, or severe renal impairment, as shown in the present study, suggests that the safety profile of the 3D or 2D regimens in such patients should be similar to that in individuals with normal renal function.

Given the single-dose treatment evaluated in this study and the low number of females who were enrolled, further evaluation with steady-state dosing is necessary to fully assess the safety and tolerability of the 3D and 2D regimens in subjects with renal impairment. One such ongoing phase IIIb study is evaluating the efficacy, safety, and pharmacokinetics of ombitasvir/paritaprevir/r plus dasabuvir with or without ribavirin in treatment-naïve patients with HCV GT1 and CKD (RUBY-I; ClinicalTrials.gov Identifier: NCT02207088). The RUBY-I study is enrolling patients with severe renal impairment or end-stage renal disease, including those receiving hemodialysis.

Two other approved DAAs that are used in the treatment of HCV (boceprevir and telaprevir) have shown modest alterations in drug exposure in subjects with severe renal impairment or end-stage renal disease that are not considered to be clinically relevant [27–29]. Notably, both boceprevir and telaprevir are administered in conjunction with ribavirin and peginterferon alfa, and are limited in applicability due to the safety/tolerability considerations and contraindications associated with interferon-based therapies [30, 31]. Similar qualifications are applicable to the DAAs simeprevir and daclatasvir, which do not require dose adjustment in renally impaired patients [32–34], yet are indicated for use in conjunction with either sofosbuvir or peginterferon alfa and ribavirin, thereby subjecting both agents to the limitations of these concomitant therapies [32, 34]. An interferon-free, two-drug combination of ledipasvir and sofosbuvir is approved for the treatment of HCV GT1; however, marked increases in drug exposure (up to 20-fold) have been observed in subjects with severe renal impairment or end-stage renal disease, and no dose recommendations are given for these patient populations [5]. Further data from the ongoing RUBY-I study will elucidate the possible role of the 3D regimen as an interferon-free DAA treatment option for subjects with HCV GT1 infection and severe renal impairment or end-stage renal disease.

The limitations that influence the interpretation or applicability of the results of this study, namely the single-dose study design, which does not address potential drug accumulation, the underrepresentation of females, and effects of potential increases in ritonavir exposures, will largely be addressed by the ongoing RUBY-I study. It will expand on the single-dose observations from this study by providing information on multiple-dose pharmacokinetics of the 3D regimen at steady state in subjects with CKD. Moreover, results from the RUBY-I study will provide efficacy data for the 3D regimen in patients with HCV and renal impairment, as well as information on the longer-term (12–24 weeks) safety profile in patients with kidney disease, including those on hemodialysis, a patient group that was not evaluated in the current study.

5 Conclusion

These single-dose evaluations suggest that no dose adjustment for the 3D (ombitasvir/paritaprevir/r plus dasabuvir) or 2D (ombitasvir/paritaprevir/r) regimens is necessary in subjects with mild, moderate, or severe renal impairment.

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Compliance with Ethical Standards

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Conflict of interest Amit Khatri, Sandeep Dutta, Lino Rodrigues Jr., Haoyu Wang, Walid M. Awni, and Rajeev M. Menon are employees of AbbVie and may hold AbbVie stocks or options. Thomas C. Marbury is an employee of Orlando Clinical Research Center, Orlando, FL, USA, and Richard A. Preston is faculty at the Miller School of Medicine, University of Miami, Miami, FL, USA.

Ethical approval This study was conducted in accordance with the Good Clinical Practice Guideline as defined by the International Conference on Harmonisation, the Declaration of Helsinki, and all applicable federal and local regulations. The study was approved by independent institutional review boards.

Informed consent Written informed consent was obtained from each subject before any study-related procedures were performed.

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