Effect of Telaprevir on the Pharmacokinetics of Cyclosporine and Tacrolimus

Varun Garg,[1] Rolf van Heeswijk,[2] Jee Eun Lee,[1] Katia Alves,[1] Priya Nadkarni,[1] and Xia Luo[1]

The hepatitis C virus protease inhibitor telaprevir is an inhibitor of the enzyme cytochrome P450 3A, responsible for the metabolism of both cyclosporine and tacrolimus. This Phase I, open-label, nonrandomized, single-sequence study assessed the effect of telaprevir coadministration on the pharmacokinetics of a single dose of either cyclosporine or tacrolimus in two separate panels of 10 healthy volunteers each. In Part A, cyclosporine was administered alone as a single 100-mg oral dose, followed by a minimum 8-day washout period, and subsequent coadministration of a single 10-mg oral dose of cyclosporine with either a single dose of telaprevir (750 mg) or with steady-state telaprevir (750 mg every 8 hours [q8h]). In Part B, tacrolimus was administered alone as a single 2-mg oral dose, followed by a minimum 14-day washout period, and subsequent coadministration of a single 0.5-mg dose of tacrolimus with steady-state telaprevir (750 mg q8h). Coadministration with steady-state telaprevir increased cyclosporine dose-normalized (DN) exposure ($DN\_AUC_{0-\infty}$) by approximately 4.6-fold and increased tacrolimus $DN\_AUC_{0-\infty}$ by approximately 70-fold. Coadministration with telaprevir increased the terminal elimination half-life ($t_{1/2}$) of cyclosporine from a mean (standard deviation [SD]) of 12 (1.67) hours to 42.1 (11.3) hours and $t_{1/2}$ of tacrolimus from a mean (SD) of 40.7 (5.85) hours to 196 (159) hours. *Conclusion*: In this study, telaprevir increased the blood concentrations of both cyclosporine and tacrolimus significantly, which could lead to serious or life-threatening adverse events. Telaprevir has not been studied in organ transplant patients; its use in these patients is not recommended because the required studies have not been completed to understand appropriate dose adjustments needed for safe coadministration of telaprevir with cyclosporine or tacrolimus, and regulatory approval has not been obtained. (HEPATOLOGY 2011;54:20-27)

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Abbreviations: AUC, area under the curve; $AUC_{0-\infty}$, area under the curve from time 0 to infinity; CI, confidence interval(s); CL/F, apparent clearance; C_{max}, maximum concentration; CRU, Clinical Research Unit; CYP3A, cytochrome P450 3A; DN, dose-normalized; F, oral bioavailability; GLS mean ratio(s), geometric least squares mean ratio(s); HCV, hepatitis C virus; λ_z, terminal elimination rate constant; P-gp, p-glycoprotein; PK, pharmacokinetic(s); q8h, every eight hours; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach maximum concentration; V_z/F, apparent volume of distribution.

From the [1]Vertex Pharmaceuticals Inc., Cambridge, MA; and [2]Tibotec BVBA, Beerse, Belgium.

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Address reprint requests to: Varun Garg, Clinical Trials and Medical Information, Vertex Pharmaceuticals Incorporated, 130 Waverly St, Cambridge, MA, 02139. E-mail: medicalinfo@vrtx.com; fax: 510-595-8183.

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The global prevalence of hepatitis C virus (HCV) infection is estimated to be 130 to 170 million, with approximately 3 to 4 million persons newly infected annually.[1,2] Approximately 38,000 new HCV cases occur annually in the United States alone.[3] An estimated 75%-85% of infected individuals who do not clear the virus by 6 months develop chronic hepatitis that is often associated with serious liver disease.[4,5] Cirrhosis develops in 4%-20% of patients with chronic HCV infection, leading to hepatocellular carcinoma at an annual rate of 1%-5%.[6] Furthermore, cirrhosis due to chronic HCV infection is the leading cause for liver transplantation; the incidence of such cases in the United States and Europe as of 2005 was approximately 30%-50%.[7]

Standard treatment for chronic HCV infection includes a combination of pegylated interferon and ribavirin, shown to cause sustained viral response in 45%-50% of patients treated.[8-10] In recent clinical studies, the coadministration of telaprevir, an HCV

protease inhibitor, with pegylated interferon/ribavirin resulted in substantial improvements in sustained viral response compared with pegylated interferon/ribavirin alone in patients with genotype 1 chronic HCV infection (treatment-naïve patients and in patients who had failed prior standard treatment).[11-15] Patients who are not eligible for standard treatment often require liver transplant due to accompanying comorbid conditions.[16] Recurrence of HCV infection occurs in 100% of liver transplantations if not eradicated prior to transplantation.[17] Cyclosporine and tacrolimus are immunosuppressants with narrow therapeutic ranges used in the postoperative phase of liver or kidney transplants to prevent allograft rejection. Cyclosporine and tacrolimus are substrates of both cytochrome P450 3A (CYP3A), the primary enzyme responsible for their metabolism,[18,19] and P-glycoprotein (P-gp), a transmembrane transporter.[20,21] Telaprevir is a CYP3A4 substrate and inhibitor and has the potential to saturate or inhibit P-gp in the gut (data on file, Vertex Pharmaceuticals Inc.). Therefore, coadministration with telaprevir may increase the systemic exposure to cyclosporine and tacrolimus. The current study was designed to gain an understanding of the effect of telaprevir on the single-dose pharmacokinetic (PK) parameters of tacrolimus and cyclosporine to provide guidance for dose adjustments of these drugs prior to initiation of trial(s) in transplant patients.

Materials and Methods

Materials. Telaprevir 375 mg tablets were manufactured at Patheon (Mississauga, Ontario, Canada). Cyclosporine 100 mg/mL solution (Neoral Novartis Pharmaceuticals, East Hanover, NJ) and tacrolimus 0.5 mg capsules (Prograf, Astellas Pharmaceuticals, Deerfield, IL) were obtained from commercial suppliers.

Human Volunteers. Study VX09-950-021 (clinical trial registration number: NCT01038167) enrolled 20 volunteers at Covance Clinical Research Unit (CRU) Dallas, Texas. Healthy males and females between 18-60 years of age with body mass index from 18.0-30.0 kg/m^2 were included. At screening, volunteers had no major or clinically significant medical history; no clinically significant abnormal results from physical examination and 12-lead electrocardiogram readings; and no out-of-range results from hematology tests, clinical chemistry, coagulation tests, and urinalysis. The systolic blood pressure for all volunteers was between 90-130 mmHg, diastolic blood pressure was between 55-90 mmHg, and supine heart rate was between 45-100 beats per minute (all limits inclusive). All volunteers were able to understand and comply with protocol requirements and signed the informed consent form prior to any study procedure. The protocol and informed consent form were approved by the Covance Ethics Committee in accordance with national procedures. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations.

Study Design. This was a Phase I, open-label, nonrandomized, single-sequence study that included screening, a dosing period, and a follow-up visit. This study had two parts: 10 volunteers were enrolled each in Parts A and B to examine the effect of telaprevir on the PK of cyclosporine and tacrolimus, respectively. Volunteers were enrolled in either Parts A or B in parallel. Assuming an expected ratio of 1.0 for mean exposure (dose-normalized), a sample size of eight volunteers was considered sufficient to achieve the 90% confidence interval (CI) within the no-effect limits of 0.80-1.25 on the Geometric Least Squares (GLS) mean ratios of the area under the curve (AUC) and the maximum concentration (C_{max}) of cyclosporine or tacrolimus following coadministration with telaprevir (test) over administration of cyclosporine or tacrolimus alone (reference).

Part A: Cyclosporine Treatment. The effect of telaprevir on cyclosporine PK was studied after a single dose and at steady-state telaprevir. During period 1, volunteers were admitted to the CRU on day −1 and discharged on day 3. On day 1, a single 100-mg oral dose of cyclosporine (1 mL Neoral oral solution, 100 mg/mL) was administered 2.5 hours after the start of a standard, medium-fat breakfast. There was a minimum washout of 8 days between day 1, period 1 and day 1, period 2. During period 2, volunteers were admitted to the CRU on day −1 and discharged on day 4. Volunteers were readmitted on day 7 and discharged on day 11. From day 1 to day 11, telaprevir 750-mg oral dose every 8 hours (q8h) was administered 0.5 hours after the start of a meal or snack. On days 1 and 8, a single 10-mg oral cyclosporine dose (100 μL Neoral oral solution, 100 mg/mL) was administered 2.5 hours after the start of a standard, medium-fat breakfast (i.e., 2 hours post-telaprevir dose). Volunteers returned for a follow-up visit on day 21 ($\pm$3 days).

Approximately 4 mL blood was drawn by venipuncture or indwelling catheter at each timepoint and processed for analyzing whole blood cyclosporine concentrations and plasma telaprevir concentrations. When cyclosporine was administered alone, blood samples were collected for cyclosporine analysis on day 1, period 1 (sampling timepoints: predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, and 48 hours

postdose). When cyclosporine was coadministered with telaprevir, blood samples were collected for cyclosporine analysis on days 1 and 8, period 2 (sampling timepoints: predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 96 hours postdose). For telaprevir concentration analysis, blood samples were drawn on day 1 and day 8, period 2 (sampling timepoints: predose, 0.5, 1, 2, 2.5, 3, 4, 6, and 8 hours post-morning dose).

Part B: Tacrolimus Treatment. The effect of telaprevir on tacrolimus PK was studied at steady-state telaprevir. During period 1, volunteers were admitted to the CRU on day −1 and discharged on day 3. On day 1, a single 2-mg oral dose of tacrolimus (4 capsules Prograf, 0.5 mg) was administered 2.5 hours after the start of the standard, medium-fat breakfast. There was a minimum washout of 14 days between day 1, period 1 and day 1, period 2. During period 2, volunteers were admitted to the CRU on day 7 and discharged on day 11. From days 1 to 13 of period 2, telaprevir 750 mg q8h was administered 0.5 hours after the start of a meal or snack. On day 8, a single 0.5-mg oral dose of tacrolimus (1 capsule Prograf, 0.5 mg) was administered 2.5 hours after the start of a standard, medium-fat breakfast (i.e., 2 hours post-telaprevir dose). Volunteers returned for a follow-up visit on day 23 (±3 days).

Approximately 4 mL of blood was drawn by way of direct venipuncture or indwelling catheter at each timepoint and processed for analyzing whole blood tacrolimus concentrations and plasma telaprevir concentrations. When tacrolimus was administered alone, blood samples were collected for tacrolimus analysis on day 1, period 1 (sampling timepoints: predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours postdose). When tacrolimus was coadministered with telaprevir, blood samples were collected for tacrolimus analysis on day 8, period 2 (sampling timepoints: predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, and 144 hours postdose). Similarly, for telaprevir concentration analysis, blood samples were drawn on day 8, period 2 (sampling timepoints: predose, 0.5, 1, 2, 2.5, 3, 4, 6, and 8 hours post-morning dose).

Bioanalysis of Cyclosporine, Tacrolimus, and Telaprevir. Whole blood concentrations of both cyclosporine and tacrolimus and plasma telaprevir concentrations were analyzed using validated assay methods. Briefly, cyclosporine, telaprevir, and their internal standards were extracted from samples using liquid/liquid extraction. Tacrolimus and its internal standard were extracted from samples using protein precipitation followed by solid-phase extraction. After evaporation under nitrogen, the residue of each analyte was reconstituted and analyzed using liquid chromatography followed by tandem mass spectrometry with selected ion monitoring in the positive ion mode. Calibration curves for each analyte was generated using weighted ($1/x^2$) linear least-squares regression.

The lower limit of quantitation for the cyclosporine assay in whole blood was 0.5 ng/mL and linear range for the calibration curve was 0.5-200 ng/mL. The lower limit of quantitation for the tacrolimus assay was 50.0 pg/mL and linear range for the calibration curve was 50.0-10,000 pg/mL. The lower limit of quantitation for the telaprevir assay was 2.0 ng/mL and linear range for the calibration curve was 2.0-5,000 ng/mL. The assay accuracy (%bias), and precision (%RSD) of the quality control samples were within ±15%.

Pharmacokinetic Assessments and Analysis. PK parameters were determined using standard noncompartmental methods with WinNonlin v. 5.2 (Pharsight, Mountain View, CA) and summarized for each treatment. The C_{max} and time to reach maximum concentration (t_{max}) were determined directly from observed data. The terminal elimination rate constant (λ_z) was estimated using least squares regression analysis and by visualization of the terminal phase of the concentration-time data on a log-linear scale. Apparent clearance (CL/F) was calculated as Dose/$AUC_{0-\infty}$ and apparent volume of distribution (V_z/F) was calculated as Dose/λ_z ($AUC_{0-\infty}$). The terminal elimination half-life ($t_{½}$) values were calculated as $\ln(2)/\lambda_z$. The C_{max} and $AUC_{0-\infty}$ of cyclosporine and tacrolimus were also dose-normalized (DN) to 1 mg to account for different doses of these drugs administered with and without telaprevir. For all PK measurements and parameters, appropriate descriptive statistics including mean, SD, and volunteer number (n) were reported.

The effect of telaprevir on the single dose PK of cyclosporine and tacrolimus was assessed by linear mixed-effects modeling. The PK exposure parameters (C_{max} and $AUC_{0-\infty}$) with and without dose-normalization were compared statistically between cyclosporine coadministered with telaprevir (days 1 and 8, period 2) and cyclosporine administered alone (day 1, period 1). A similar statistical comparison was made between tacrolimus coadministered with telaprevir (day 8, period 2) and tacrolimus administered alone (day 1, period 1). The dose-normalization method is considered valid because the doses of cyclosporine and tacrolimus chosen for this study are within the dose proportional range.[18] Analysis of variance was performed with SAS PROC MIXED, v. 8.2 (SAS Institute, Cary, NC) on log-transformed variables with period as the fixed

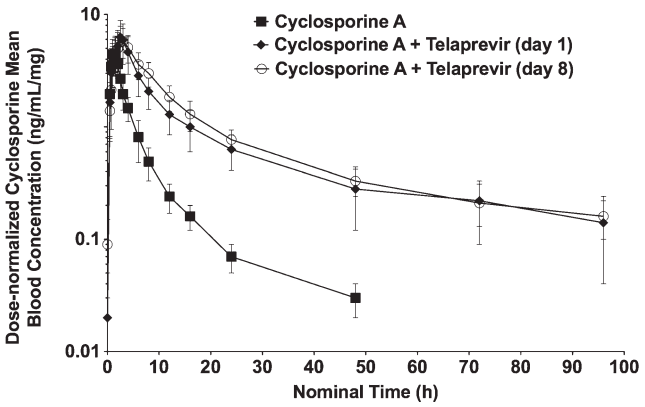

Fig. 1. Dose-normalized mean (SD) blood concentration-time profiles of cyclosporine following administration of cyclosporine alone and with telaprevir (log-linear scale).

effect and volunteer as a random effect. The GLS mean ratio indicates the fold-change in the PK parameter when telaprevir was coadministered.

Safety Assessments. For enrolled volunteers, clinical laboratory tests (hematology, serum chemistry, urinalysis), vital signs, 12-lead electrocardiograms, and adverse events were monitored throughout the study. Clinically significant abnormal laboratory findings were reported as adverse events. A follow-up visit was conducted ≈10 days following the last dose of study medication.

Results

Disposition and Demographics. The first volunteer signed the informed consent form in January 2010, and the last volunteer completed the last visit in April 2010. In Part A, all 10 volunteers received at least one dose of cyclosporine and nine volunteers received at least one dose of cyclosporine coadministered with telaprevir. Mean (SD) volunteer age was 45.8 (9.19) years, height was 167 (11.8) cm, weight was 68.5 (11.6) kg, and body mass index was 24.4 (2.56) kg/m^2. The majority of volunteers were females (70%) and white (80%).

In Part B, all 10 volunteers received at least one dose of tacrolimus administered alone and nine volunteers received at least one dose of telaprevir. One volunteer was withdrawn due to noncompliance with study procedures. Mean (SD) volunteer age was 38.0 (11.0) years, height was 175 (6.73) cm, weight was 77.4 (11.7) kg, and body mass index was 25.4 (3.53) kg/m^2. All volunteers were male (100%) and the majority were white (70%).

Cyclosporine Pharmacokinetics. The dose-normalized mean (SD) blood concentration-time profiles for cyclosporine administered either alone (day 1, period 1) or with telaprevir (days 1 and 8, period 2) are presented in Fig. 1. The dose-normalized concentrations of cyclosporine were higher when coadministered with telaprevir than for cyclosporine administered alone. Without dose normalization, the cyclosporine concentrations were lower when coadministered as a 10-mg dose with telaprevir than following administration of a 100-mg dose of cyclosporine alone (concentration-time profile without dose normalization not shown). Cyclosporine concentration-time profiles were comparable on day 1, period 2 and day 8, period 2, when a 10-mg dose of cyclosporine was administered with either a single dose of telaprevir or at steady-state telaprevir.

The mean (SD) PK and statistical parameters for cyclosporine administered either alone (100-mg dose;

Table 1. Mean (SD) of PK Parameters and Statistical Analysis of Cyclosporine Following Administration of Cyclosporine Alone (Day 1, Period 1) and with Telaprevir (Day 1 and Day 8, Period 2)

	Cyclosporine 100 mg (n = 10)	Cyclosporine 10 mg + Telaprevir Day 1 (n = 9)		Cyclosporine 10 mg + Telaprevir Day 8 (n = 9)	
PK Parameter	Mean (SD)	Mean (SD)	GLS Mean Ratio‡ (90% CI)	Mean (SD)	GLS Mean Ratio‡ (90% CI)
$AUC_{0-\infty}$ (ng·hr/mL)*	1880 (489)	805 (306)	0.41 (0.35, 0.49)	853 (218)	0.46 (0.39, 0.55)
$DN\_AUC_{0-\infty}$ (ng·hr/mL/mg)*	18.8 (4.89)	80.5 (30.7)	4.11 (3.49, 4.85)	85.3 (21.8)	4.64 (3.90, 5.51)
C_{max} (ng/mL)	489 (142)	65.7 (24.9)	0.14 (0.11, 0.17)	62.2 (18.9)	0.13 (0.11, 0.16)
DN_C_{max} (ng/mL/mg)	4.89 (1.42)	6.57 (2.49)	1.36 (1.12, 1.65)	6.22 (1.89)	1.32 (1.08, 1.60)
$t_{1/2}$ (hr)*	12.0 (1.67)	52.5 (20.5)	–	42.1 (11.3)	–
t_{max} (hr)†	1.50 (0.75, 2.00)	2.50 (2.50, 4.28)	–	2.50 (1.50, 3.05)	–
V_z/F (L)*	955 (195)	1010 (444)	–	735 (198)	–
CL/F (L/hr)*	56.3 (14.0)	14.3 (5.86)	–	12.5 (3.33)	–

Abbreviations: DN_, dose-normalized; n, number of volunteers.

*n = 9 for cyclosporine (100-mg dose) arm and cyclosporine (10-mg dose) and telaprevir coadministration on Day 1 arm; n = 8 for cyclosporine (10-mg dose) and telaprevir coadministration on Day 8 arm, as values were excluded due to Rsq <0.9 for estimation of λ_z.

†Median (min, max).

‡Value corresponding to 10-mg cyclosporine + telaprevir (either Day 1 or Day 8 as applicable) is used as the numerator (test) and value corresponding to 100-mg cyclosporine administered alone is used as the denominator (reference).

– Not applicable.

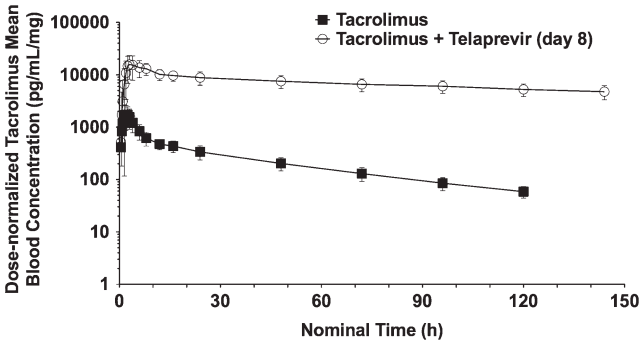

Fig. 2. Dose-normalized mean (SD) blood concentration-time profiles of tacrolimus following administration of tacrolimus alone and with telaprevir (log-linear scale).

day 1, period 1) or with telaprevir (10-mg dose; days 1 and 8, period 2) are summarized in Table 1. In Part A, a comparison of PK parameters when cyclosporine was administered alone versus coadministered with telaprevir indicated that median t_{max} of cyclosporine increased from 1.50 hours on day 1, period 1 to 2.50 hours on both days 1 and 8, period 2; mean V_z/F changed from 955 L on day 1, period 1 to 1,010 L on day 1, period 2 and 735 L on day 8, period 2; mean CL/F decreased from 56.3 L/h on day 1, period 1 to 14.3 L/h on day 1, period 2 and 12.5 L/h on day 8, period 2; and mean $t_{½}$ increased from 12.0 hours on day 1, period 1 to 52.5 hours on day 1, period 2 and 42.1 hours on day 8, period 2. The DN_C_{max} GLS mean ratios (90% CI) for cyclosporine coadministered with telaprevir were 1.36 (1.12, 1.65) on day 1, period 2 and 1.32 (1.08, 1.60) on day 8, period 2 compared to cyclosporine administered alone. Similarly, the DN_$AUC_{0-\infty}$ GLS mean ratios (90% CI) for cyclosporine coadministered with telaprevir were 4.11 (3.49, 4.85) on day 1, period 2 and 4.64 (3.90, 5.51) on day 8, period 2 compared to cyclosporine administered alone on day 1, period 1, indicating a significant effect of a single dose and steady-state telaprevir on the PK of cyclosporine.

Tacrolimus Pharmacokinetics. The dose-normalized mean (SD) blood concentration-time profiles for tacrolimus administered either alone (2-mg dose; day 1, period 1) or with telaprevir (0.5-mg dose; day 8, period 2) are presented in Fig. 2. Tacrolimus concentrations were considerably higher when coadministered with telaprevir than for tacrolimus administered alone.

The mean (SD) PK and statistical parameters for tacrolimus administered either alone (2-mg dose; day 1, period 1) or with telaprevir (0.5-mg dose; day 8, period 2) are summarized in Table 2. In Part B, a comparison of PK parameters when tacrolimus was administered alone versus coadministered with telaprevir indicated that median t_{max} of tacrolimus increased from 2.25 hours on day 1, period 1 to 3.03 hours on day 8, period 2; mean V_z/F decreased from 1,910 L on day 1, period 1 to 106 L on day 8, period 2; mean CL/F decreased from 32.0 L/h on day 1, period 1 to 0.48 L/h on day 8, period 2; and mean $t_{½}$ increased from 40.7 hours on day 1, period 1 to 196 hours on day 8, period 2. The DN_C_{max} GLS mean ratio (90% CI) for tacrolimus coadministered with telaprevir was 9.35 (6.73, 13.0) on day 8, period 2 compared to tacrolimus administered alone (day 1, period 1). Similarly, the DN_$AUC_{0-\infty}$ GLS mean ratio (90% CI) for tacrolimus coadministered with telaprevir was 70.3 (52.9, 93.4) on day 8, period 2 compared to tacrolimus administered alone (day 1, period 1), indicating a significant effect of telaprevir on the PK of tacrolimus.

Plasma Pharmacokinetics of Telaprevir. Mean (SD) PK parameters for telaprevir when coadministered with either cyclosporine or tacrolimus are shown in Table 3. Steady-state concentrations of telaprevir on day 8, period 2 were similar when telaprevir was coadministered with either cyclosporine or tacrolimus. Steady-state exposure of telaprevir reported in this study was comparable with historical data.[22]

Safety. In Part A, adverse events of mild vessel puncture site pain (n = 1), mild pharyngitis (n = 1), mild accidental needle stick (n = 1), and moderate neutropenia (n = 1) occurred when cyclosporine was administered alone. Moderate neutropenia led to premature discontinuation of the volunteer from the

Table 2. Mean (SD) PK Parameters and Statistical Analysis of Tacrolimus Following Administration of Tacrolimus Alone (Day 1, Period 1) and with Telaprevir (Day 8, Period 2)

	Tacrolimus 2 mg (n = 10)	Tacrolimus 0.5 mg + Telaprevir Day 8 (n = 9)	
PK Parameter	Mean (SD)	Mean (SD)	GLS Mean Ratio‡ (90% CI)
$AUC_{0-\infty}$ (ng·hr/mL)*	67.3 (17.3)	1310 (866)	17.6 (13.2, 23.3)
DN_$AUC_{0-\infty}$ (ng·hr/mL/mg)*	33.6 (8.64)	2620 (1730)	70.3 (52.9, 93.4)
C_{max} (ng/mL)	3.97 (1.82)	8.70 (3.23)	2.34 (1.68, 3.25)
DN_C_{max} (ng/mL/mg)	1.99 (0.91)	17.4 (6.47)	9.35 (6.73, 13.0)
$t_{½}$ (hr)*	40.7 (5.85)	196 (159)	–
t_{max} (hr)†	2.25 (1.50, 12.0)	3.03 (2.50, 24.0)	–
V_z/F (L)*	1910 (859)	106 (34.2)	–
CL/F (L/hr)*	32.0 (10.2)	0.48 (0.19)	–

Abbreviations: DN_, dose-normalized; n, number of volunteers.

*λ_z related parameters should be interpreted with caution, since the extrapolated AUC was greater than 25%. n = 8 for tacrolimus (0.5-mg dose) and telaprevir coadministration arm, as one value was excluded due to Rsq <0.9 for estimation of λ_z.

†Median (min, max).

‡Value corresponding to 0.5-mg tacrolimus + telaprevir (Day 8) is used as the numerator (test) and value corresponding to 2-mg tacrolimus administered alone is used as the denominator (reference).

– Not applicable.

Table 3. Mean (SD) of Telaprevir PK Parameters Following Coadministration of Telaprevir with Cyclosporine or with Tacrolimus

	Part A		Part B
PK Parameter	Telaprevir Day 1+ Cyclosporine (n = 10)	Telaprevir Day 8 + Cyclosporine (n = 9)	Telaprevir Day 8 + Tacrolimus (n = 9)
Telaprevir			
$AUC_{0\text{-}8hr}$ (ng·hr/mL)	9360 (3560)	21900 (2810)	16600 (3340)
C_{max} (ng/mL)	2170 (830)	3432 (543)	2500 (626)
C_{min} (ng/mL)	NA	2170 (283)	1720 (439)
t_{max} (hr)*	4.00 (2.50, 7.92)	3.00 (1.92, 6.00)	4.00 (0.00, 4.10)

Abbreviations: n, number of volunteers; NA, not applicable.
*Median (min, max).

study. Adverse events of mild dyspepsia (n = 1); mild rash (n = 2); mild herpes simplex (n = 1); mild contusion (n = 1); mild blood creatine phosphokinase increase (n = 1); mild somnolence (n = 1); and mild vaginal discharge (n = 1) occurred when cyclosporine was coadministered with telaprevir. Dyspepsia and rash were considered by the study investigator to be possibly related to the study drugs.

In Part B, an adverse event of mild constipation (n = 1) occurred when tacrolimus was administered alone. Adverse events of mild pruritus (n = 1) and mild excoriation (n = 1) occurred when tacrolimus was coadministered with telaprevir.

No serious, life-threatening, or severe adverse events occurred in any group. There were no notable clinically significant trends for any of the chemistry parameters, hematology parameters, vital signs, 12-lead electrocardiograms, or physical examination findings.

Discussion

The primary objective of this study was to evaluate the effect of telaprevir on the PK of single doses of cyclosporine and tacrolimus in healthy volunteers. The 100-mg cyclosporine dose and the 2-mg tacrolimus dose were chosen as they were well tolerated in healthy volunteers in previous studies.[23,24] The doses of cyclosporine and tacrolimus were lowered when coadministered with telaprevir because of the potential for marked increase in cyclosporine and tacrolimus exposure.

Dose-normalized cyclosporine exposure increased significantly when coadministered with telaprevir compared to administration of cyclosporine alone: the dose-normalized C_{max} increased by approximately 1.3- to 1.4-fold, dose-normalized AUC increased by approximately 4.1- to 4.6-fold, and mean $t_{½}$ of cyclosporine increased approximately 4-fold following coadministration of cyclosporine with either a single dose or steady-state telaprevir. Cyclosporine exposure was comparable when administered with either a single dose of telaprevir (day 1, period 2) or when telaprevir reached steady-state (day 8, period 2), suggesting an absence of time-dependent inhibition of cyclosporine metabolism by telaprevir.

The effect of telaprevir coadministration was much greater with tacrolimus: the dose-normalized C_{max} increased by approximately 9.3-fold, dose-normalized AUC increased by approximately 70-fold, and the mean $t_{½}$ of tacrolimus increased approximately 5-fold. Because of the long $t_{½}$ of tacrolimus and the long time it would take to wash out any effect of telaprevir on its PK, the interaction with tacrolimus was only evaluated with steady-state telaprevir. It is unknown whether the magnitude of the effect of telaprevir on tacrolimus would be similar after the first dose of telaprevir, as seen with cyclosporine.

These results are significant and indicate that without understanding the adjustments required for dose and/or dosing frequency of cyclosporine and tacrolimus, telaprevir coadministration could lead to serious or life-threatening adverse events. The mechanism for the greater effect of telaprevir on the PK of tacrolimus compared to cyclosporine is unknown, but may be related to lower bioavailability of tacrolimus (≈18%) in healthy volunteers,[19] making it more susceptible to CYP3A and/or P-gp inhibition in the gut and during first-pass metabolism. This is also suggested by the 9.3-fold increase in the tacrolimus C_{max} and the sharp decrease in the mean (SD) apparent volume of distribution (Vz/F) of tacrolimus from 1,910 (859) L when administered alone to 106 (34) L (Table 2) in the presence of telaprevir (i.e., an increase in oral bioavailability, F, without a proportional change in volume of distribution, Vz, may decrease the ratio, Vz/F closer to the reported value of Vz, corrected for F, in healthy volunteers of 1.94 L/kg[19]). In contrast, there was no apparent change in the Vz/F of cyclosporine after the first or last telaprevir dose (Table 1) compared to cyclosporine administered alone, suggesting that bioavailability of cyclosporine was not changed in the presence of telaprevir, consistent with the observed modest effect of telaprevir on the C_{max} of cyclosporine. However, the bioavailability of cyclosporine varies considerably depending on patient population (ranging from <10% in liver transplant patients to 89% in some kidney transplant patients).[18] Therefore, the effect of telaprevir on cyclosporine concentrations in liver transplant patients may differ from that observed in this

healthy volunteer study, and close monitoring of cyclosporine concentrations to guide individual dose adaptations would be necessary during coadministration.

The decrease in hepatic clearance and increase in $t_{1/2}$ of both cyclosporine and tacrolimus upon telaprevir coadministration suggests that systemic clearance of these immunosuppressants was also reduced by telaprevir. The effect of telaprevir on hepatic transporters that could have contributed to lower clearance or enhanced absorption is unknown.

Notably, in this study the effect of steady-state telaprevir on the PK of cyclosporine or tacrolimus was evaluated only at single doses of these immunosuppressants. Because the elimination half-lives increased significantly for both cyclosporine and tacrolimus when telaprevir was coadministered, without proper adjustment of dose and dosing interval of these immunosuppressants, further increases in blood exposure may occur when multiple doses of these drugs are coadministered with telaprevir. However, studies of telaprevir with multiple doses of cyclosporine and tacrolimus have not been performed.

The effects of telaprevir on cyclosporine and tacrolimus exposure were similar to that reported for human immunodeficiency virus (HIV) protease inhibitors known to be potent CYP3A inhibitors, where significant reductions in dose and/or dosing interval of immunosuppressants were needed to achieve the desired range of trough concentrations, based on frequent monitoring of trough concentrations of the immunosuppressants.[25] For example, addition of lopinavir/ritonavir ($n = 7$ patients) reduced tacrolimus dose by 99% to maintain tacrolimus concentrations within the therapeutic range.[26] Similarly, during coadministration of Highly Active Antiretroviral Therapy (HAART) regimens with ritonavir-boosted HIV protease inhibitors, daily cyclosporine doses were reduced by 80%-95% to maintain cyclosporine exposure at pre-HAART levels. Because of the flat absorption/elimination profiles of cyclosporine during combination with ritonavir-boosted HAART therapy, cyclosporine exposure could be reliably monitored long-term by measuring cyclosporine trough concentrations.[27] Treatment of post-transplant patients coinfected with HIV/HCV with antiretrovirals and telaprevir could be even more challenging, depending on the drugs involved. Telaprevir levels are not significantly affected by ritonavir[28]; however, whether the net effect of antiretroviral drugs on cyclosporine and tacrolimus PK would be similar or different is hard to predict, as these drugs may have their own effects. The PK of tacrolimus and cyclosporine may also vary based on CYP3A5 genotype.[29] Therefore, the effect of telaprevir on these drugs may also vary based on CYP3A5 genotype.

Although cyclosporine is a CYP3A and P-gp inhibitor,[18] the effects of a single cyclosporine dose on systemic telaprevir exposure were considered negligible, because the cyclosporine dose (10 mg) was low and administered 2 hours after telaprevir administration. This study was not designed to test the effect of cyclosporine and tacrolimus on telaprevir exposure. However, telaprevir steady-state exposure in Parts A and B were similar to previous Phase I studies,[22] so it is unlikely that coadministration of cyclosporine or tacrolimus had a relevant effect on telaprevir exposure.

Food decreases cyclosporine and tacrolimus exposure (C_{max} by 33% and 65%; AUC by 13% and 28%, respectively),[18,19] whereas telaprevir exposure increases with food. Telaprevir was administered 30 minutes after the start of a meal and cyclosporine or tacrolimus were administered 2 hours after telaprevir during coadministration. Volunteers refrained from further food or drink during the period between administration of telaprevir and cyclosporine or tacrolimus. This approach was used to minimize food effect on cyclosporine and tacrolimus exposure, while providing appropriate telaprevir dosing conditions. The extent to which simultaneous telaprevir administration with cyclosporine or tacrolimus in the fed state would impact these results is unknown.

Another important consideration about concomitant tacrolimus or cyclosporine use with telaprevir in organ transplant patients is that after telaprevir treatment is completed or stopped, its inhibitory effect on CYP3A/P-gp would wear off and doses of immunosuppressant would need readjustments. Estimates of the recovery time of CYP3A activity vary widely[30] and precise timing for CYP3A activity to resume to the levels before the start of telaprevir is unknown. Therefore, careful blood concentration monitoring of immunosuppressants will be needed for approximately 2 weeks after telaprevir is stopped.

Besides cyclosporine and tacrolimus, other immunosuppressants that are likely to have a significant interaction with telaprevir include those known to have increased exposures when coadministered with strong CYP3A inhibitors, such as sirolimus and everolimus. Exposure of corticosteroids known to be metabolized by way of CYP3A may also increase in the presence of strong CYP3A inhibitors. However, studies with these drugs in combination with telaprevir have not been conducted.

Finally, telaprevir has not been studied in pre-, post-, or peritransplant patients. The degree of the interaction

with calcineurin inhibitors reported here suggests potential implications for patient safety. Telaprevir should not be administered to these patients, because the required studies have not been completed to understand appropriate dose adjustments needed for safe coadministration of telaprevir with cyclosporine or tacrolimus, and regulatory approval has not been obtained.

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