Pharmacokinetics of Treprostinil Diolamine in Subjects With End-Stage Renal Disease On or Off Dialysis

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Abstract: Treprostinil diolamine sustained release (UT-15C SR) is being evaluated as an oral therapy for pulmonary arterial hypertension. This study evaluated the pharmacokinetics (PKs) of treprostinil following administration of UT-15C SR in subjects with end-stage renal disease (ESRD) compared with healthy subjects with normal renal function (NRF) and the effect of hemodialysis on the PK parameters of treprostinil. Eight ESRD subjects (requiring dialysis, mean creatinine clearance = 11.5 mL/min) received 2 single doses of 1 mg of UT-15C SR (separated by 2 weeks), with the first dose given immediately after dialysis and the second given 4 hours before the start of dialysis. Eight NRF subjects received a single dose of 1 mg of UT-15C SR. The median C_{max}, AUC_{0-inf}, and $t_{1/2}$ of treprostinil were 680 pg/mL, 3240 hours·pg/mL, and 2.35 hours, respectively, in ESRD subjects dosed after dialysis and were 551 pg/mL, 3152 hours·pg/mL, and 2.05 hours, respectively, in ESRD subjects dosed before dialysis. In comparison, corresponding values were 730 pg/mL, 3726 hours·pg/mL, and 3.54 hours, respectively, in NRF subjects. UT-15C SR of 1 mg was well tolerated by NRF and ESRD subjects. The most frequent adverse event was headache and nausea. There was no substantial difference in treprostinil PKs between ESRD and NRF subjects following administration of UT-15C SR tablets. Hemodialysis did not have clinically important effect on treprostinil PK in ESRD subjects.

Key Words: treprostinil, pulmonary arterial hypertension, pharmacokinetics, renal impairment, end-stage renal disease, hemodialysis

(*J Cardiovasc Pharmacol*™ 2013;61:272–276)

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a life-threatening disease with no known cure. There are 3 major factors thought to contribute to the increased pulmonary vascular resistance seen in this disease: vasoconstriction, remodeling of the vessel wall, and thrombosis.[1,2] Treprostinil is a chemically stable prostacyclin analogue. As the sodium salt, it is commercially available formulations for parenteral (Remodulin) and inhaled (Tyvaso) use for the treatment of PAH. The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, inhibition of platelet aggregation, and antiproliferative effects.

Treprostinil diolamine (UT-15C) is a salt form of treprostinil, which has been formulated into an oral sustained release (SR) tablet and is currently under development for the treatment of PAH. After a single oral dose of UT-15C in healthy human subjects, the majority of the dose was recovered in urine as the metabolites of treprostinil, with less than 1% of the dose excreted unchanged in urine. Thus, metabolism is the primary elimination pathway for treprostinil and urinary excretion is a minor pathway. In vitro data suggest that treprostinil is primarily metabolized by cytochrome P450 isozyme CYP2C8 and to a lesser extent by CYP2C9. Patients with PAH commonly present with comorbidities including renal dysfunction.

In general, renal impairment can affect the excretion of a drug and/or its metabolites especially when they are primarily eliminated by urinary excretion. Nonetheless, renal impairment can adversely affect some pathways of hepatic/gut wall metabolism and can be associated with other changes in drug disposition, such as changes in absorption, plasma protein binding, and transport or distribution.[3,4] These changes may be particularly prominent in patients with severely impaired renal function and have been observed even when renal excretion is not the primary route of elimination. This subset of patients frequently is excluded from pivotal clinical trials, resulting in little safety and efficacy data for patients with severe renal impairment. Therefore, understanding whether treprostinil pharmacokinetics (PK) would be altered in subjects with renal impairment is important in assessing the safety of using UT-15C SR in this patient cohort.

This study was designed to evaluate the effect of renal dysfunction on the PK of treprostinil following administration of UT-15C SR. The design was based upon the Reduced PK Study Design outlined in the Food and Drug Administration (FDA) Guidance "Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling."[5] The rationale for using the "Reduced PK Study Design" was that treprostinil is predominantly metabolized, so it is expected that renal impairment may not substantially affect treprostinil PK. Thus, the study was carried out by first evaluating the "worst case," that is, to enroll subjects with end-stage renal disease (ESRD), the most severe case of renal impairment, and then comparing treprostinil PKs between ESRD subjects and healthy subjects with normal

Received for publication October 1, 2012; accepted November 14, 2012.
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United Therapeutics funded the conduct of the study.
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renal function (NRF). In addition, the effect of hemodialysis on treprostinil PKs in ESRD subjects was also evaluated.

METHODS

This phase I, single-site, open-label, single-dose study was designed based upon the FDA Guidance for assessing drug PKs in subjects with impaired renal dysfunction.[5] The study was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines, and the protocol was approved by Independent Investigational Review Board (Plantation, FL; April 2010). All participating subjects gave written informed consent before participating in the study.

This study was designed to evaluate the PK of treprostinil after a single oral dose of UT-15C SR of 1 mg tablet in subjects with varying degrees of renal impairment, including mild, moderate, and severe impairment, and subjects with ESRD requiring dialysis in comparison with that in healthy subjects with NRF. However, a Reduced PK Study Design was carried out by enrolling the ESRD and healthy subjects first and then depending on the PK results between these 2 groups, subjects with less severe renal impairment might be enrolled for further PK assessments and comparisons. The healthy subjects were enrolled after ESRD subjects and individually matched for age (within 10 years), body mass index (BMI; within 30%), and gender of ESRD subjects. For the purposes of this study, the ESRD subjects also served as subjects with "severe" renal impairment after they had been dialyzed based on the fact that subjects with ESRD on dialysis will typically have a creatinine clearance (CLcr) between 0 and 10 mL/min, which conforms to the definition for subjects with severe renal impairment, that is, CLcr $<$ 30 mL/min. CLcr was estimated based on Cockcroft–Gault equation as follows:

$$\mathrm{CLcr} = [(140 - \mathrm{Age\ (y)}) \times \mathrm{Weight\ (kg)}]/ [\mathrm{serum\ creatinine\ (mg/dL)} \times 72](\times 0.85 \text{ for females}).$$

The mean total plasma exposure to treprostinil, as assessed by its plasma $AUC_{(0-inf)}$, in ESRD subjects was not substantially (ie, not more than 50%) different from healthy subjects (see Results), this study was terminated without enrolling subjects with less severe renal impairment (per FDA Guidance for Industry[5]).

Eligible Subjects

Eligible subjects were between 18 and 79 years of age, had a BMI between 18 and 40 kg/m^2, willing to abstain from consuming grapefruit or xanthine-containing food or beverages, and had a clinically insignificant medical history, physical examination, vital signs, electrocardiogram, and clinical laboratory results (or considered normal for subjects with renal impairment). Subjects in the severe renal dysfunction group were all diagnosed as having ESRD and currently receiving hemodialysis 3 times each week.

Subjects were excluded if they had a history of postural hypotension, unexplained syncope, a blood pressure less than 85 mm Hg systolic or 50 mm Hg diastolic, or a pulse rate greater than 95 bpm. Subjects with a history of uncontrolled hypertension or a blood pressure $>$160 mm Hg systolic or $>$90 mm Hg diastolic for subjects with NRF or a blood pressure $\geq$180 mm Hg systolic or $\geq$100 mm Hg diastolic for ESRD subjects. NRF subjects were excluded if they were taking any medications. Subjects with ESRD were excluded if any new medications were started within 21 days before dosing or if the subject was taking any CYP2C8 inducers or inhibitors or any nephrotoxic agents, including chronic nonsteroidal anti-inflammatory drug use, recent initiation of an angiotensinogen converting enzyme or any antibiotics within 1 week before baseline.

Study Procedures

Subjects with ESRD received 2 single doses of UT-15C SR of 1 mg tablet in a 2-period, single-sequence, 2-way crossover fashion. The first dose of UT-15C SR of 1 mg was given immediately (within 1 hour) after the completion of a regular hemodialysis (postdialysis) to assess the effect of severe renal impairment on the PKs of treprostinil. Two weeks later, the second dose of UT-15C SR of 1 mg tablet was given 4 hours before the start of dialysis (predialysis) to assess the effect of hemodialysis on the PKs of treprostinil. Subjects with NRF received a single dose of UT-15C SR of 1 mg tablet. A 1 mg UT-15C dose was selected for this study to ensure that treprostinil concentrations would be above the lower limit of quantification for the treprostinil LC/MS/MS assay. Furthermore, this dose was selected because single oral doses of 1 mg of UT-15C SR are generally well tolerated in healthy volunteers based on dosing of approximately 500 volunteers in previous clinical pharmacology studies.

Subjects underwent a screening exam up to 21 days before study entry. Eligible subjects were admitted to the clinical research unit the night before the treatment period(s). The next day, immediately (within 10 minutes) after consuming a standardized breakfast [~500 Calorie well-balanced meal breakfast (54% carbohydrates, 32% fat, and 14% protein)], subjects received an oral dose of UT-15C SR of 1 mg tablet. A predose blood samples were collected before dosing. Subsequently, blood samples were collected from all subjects at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36, 42, and 48 hours postdose. An additional 60-hour postdose sample was collected from subjects with ESRD receiving the dose after dialysis. Subjects remained in the clinical research unit until the final PK blood sample was collected and all end-of-study safety evaluations were performed.

Plasma Sample Analysis for Treprostinil Concentrations

Blood samples for PK evaluation were collected into a Vacutainer tube containing K_3EDTA as the anticoagulant. Plasma was separated and stored at -20°C until analysis.

Plasma samples were analyzed for concentrations of treprostinil (the free acid of treprostinil diolamine) by a validated method using solid-phase extraction followed by ultra-performance liquid chromatography coupled with tandem mass spectrometry detection. The lower limit of quantification was

TABLE 1. Summary of Baseline Demographic Characteristics

	NRF (n = 8)	ESRD (n = 8)
Age, y, mean (range)	54.4 (37–64)	53.1 (42–62)
Gender, M:F	5:3	5:3
Height, cm, mean (SD)	169.6 (±7.35) (range: 158–178)	174.4 (±7.61) (range: 164–186)
Weight, kg, mean (SD)	84.1 (±17.7) (range: 61.5–106.0)	92.2 (±23.1) (range: 64.3–124.6)
BMI, kg/m², mean (SD)	28.9 (±4.1) (range: 22.3–34.1)	30.2 (±6.8) (range: 22.8–38.9)
Ethnic origin, n (%)		
Hispanic/Latino	1 (13)	1 (13)
Not Hispanic/Latino	7 (88)	7 (88)
Race, n (%)		
American Indian/Alaskan	0	2 (25)
African American	2 (25)	7 (88)
White	6 (75)	0
CLcr, mL/min, mean (SD)	125.8 (±25.6) (range: 91.9–158.3)	11.5 (±4.5) (range: 5.8–19.8)

10 pg/mL and the linear concentration range for the calibration curve was from 10 to 5000 pg/mL. In addition, validation procedures showed that blood sample hemolysis does not affect the determination of treprostinil concentrations in plasma.

Pharmacokinetic Data Analysis

Plasma treprostinil concentration versus time data in individual subjects was subjected to noncompartmental analysis using WinNonlin (Pharsight Corporation, Mountain View, CA). The actual blood sampling time for each sample was used for data analysis. The parameters included observed maximum plasma concentration (C_{max}), the time when C_{max} was observed (t_{max}), area under the plasma concentration versus time curve (AUC) from time of dosing to the last time point with measurable treprostinil concentration (AUC_{0-t}) calculated by linear trapezoidal method and AUC from time of dosing with extrapolation to infinity (AUC_{0-inf}), and plasma half-life ($t_{1/2}$).

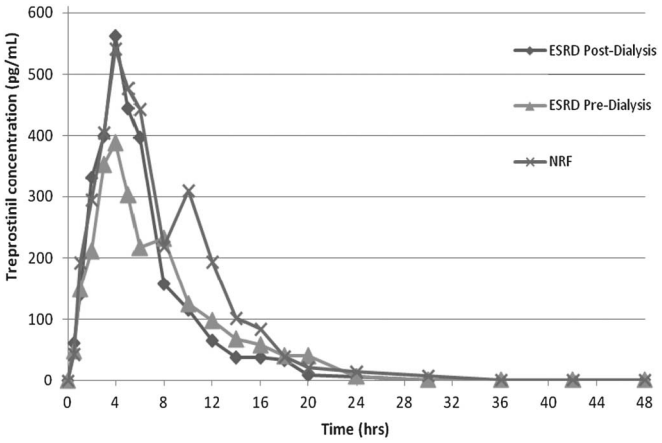

FIGURE 1. Mean plasma treprostinil concentration versus time curves.

Statistical Methods

PK parameter estimates were summarized descriptively for ESRD subjects postdialysis, ESRD subjects before dialysis, and healthy subjects with NRF. Box plots of the interquartile ranges and whiskers at 1.5, the interquartile range were used to visually compare $AUC_{(0-inf)}$, $AUC_{(0-t)}$, and C_{max} of treprostinil between dosing 4 hours before dialysis and after dialysis in ESRD subjects.

Additional analysis was performed using by analysis of covariance (ANCOVA) for comparison of $AUC_{(0-inf)}$, $AUC_{(0-t)}$, and C_{max} of treprostinil after $\log_e$ transformation between the ESRD subjects postdialysis and healthy subjects. The ANCOVA used a fixed-effect model with subject cohort as the predictor. The least squares mean difference in the parameter estimates between cohorts (ESRD postdialysis dosing vs subjects with NRF) together with the corresponding 90% confidence interval (CI) for the differences was calculated. The difference and CI were then transformed back to the original scale to provide an estimate of the geometric least squares mean (GLSM) and 90% CI as the parameter ratios, ESRD subjects versus NRF subjects.

TABLE 2. Summary of Treprostinil Pharmacokinetic Parameters

Subject Group Treatment	Statistics	C_{max} (pg/mL)	t_{max} (h)	$AUC_{(0-inf)}$ (h·pg/mL)	$t_{1/2}$ (h)
ESRD postdialysis (n = 8)	GeoMean	732	NA	3224	2.36
	CV%	56.3	NA	45.3	54.7
	Median	680	4.5	3240	2.35
	Range	310–1430	2.0–10	1919–5986	0.89–4.29
ESRD before dialysis (n = 8)	GeoMean	492	NA	2546	1.88
	CV%	54.8	NA	84.9	60.7
	Median	551	4.0	3152	2.05
	Range	248–1110	1.0–8.0	918–6853	0.78–4.19
NRF (n = 8)	GeoMean	686	NA	4180	3.18
	CV%	23.9	NA	55.9	56.2
	Median	730	5.5	3802	3.54
	Range	456–862	3.0–10	2190–8719	1.51–6.00

CV, coefficient of variation around geometric mean.

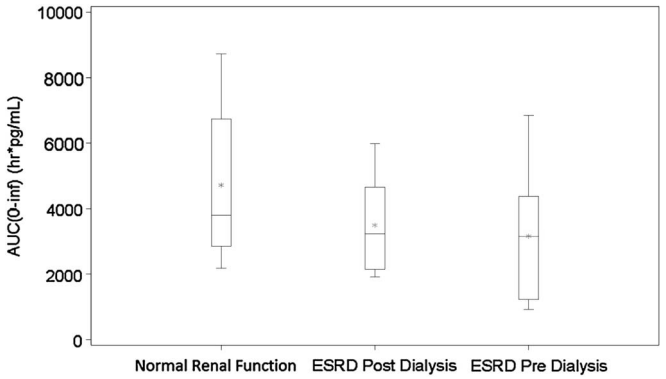

FIGURE 2. Comparative box plots of treprostinil AUC_{inf} between subject groups and treatments.

RESULTS

Subjects

A total of 8 subjects with ESRD and 8 subjects with NRF were enrolled and all subjects completed the study. The subjects with NRF were individually matched with the ESRD subjects by gender (5 males and 3 females), age (within 10 years), and BMI (within 30%). At study entry, the ESRD subjects had a mean CLcr of 11.5 mL/min (range: 5.8–19.8 mL/min) compared with a mean of 125.8 mL/min (range: 91.9–158 mL/min) for subjects with NRF. Table 1 provides additional demographic data.

Treprostinil Pharmacokinetics

Treprostinil was rapidly absorbed following administration of a 1-mg UT-15C SR tablet after consumption of a well-balanced meal in ESRD subjects dosed before or postdialysis similar to that observed in subjects with NRF. The mean plasma treprostinil profiles in ESRD subjects pre- and postdialysis and in subjects with NRF followed a similar pattern (Fig. 1). PK parameter estimates of treprostinil in each subject groups are summarized in Table 2.

The median time to maximum concentration (t_{max}) was similar between ESRD subjects dosed predialysis (4 hours) and postdialysis (4.5 hours) and subjects with NRF (5 hours). The median value of the apparent elimination half-life ($t_{1/2}$) of treprostinil was also comparable between ESRD subjects dosed before dialysis (2.1 hours) and after dialysis (2.4 hours) and NRF subjects (3.5 hours).

Median C_{max} of treprostinil was comparable between subjects with NRF (730 pg/mL) and ESRD subjects dosed postdialysis (680 pg/mL); however, there was greater variability in treprostinil C_{max} in ESRD subjects (coefficient of variation = 55%–56%) than in subjects with NRF (coefficient of variation = 24%). Median C_{max} of treprostinil in ESRD subjects dosed before dialysis (551 pg/mL) was comparable with that in ESRD subjects dosed after dialysis. Statistical analysis (ANCOVA) showed that the GLSM ratio for C_{max}, ESRD postdialysis versus NRF subjects was 1.07, with a 90% CI of 0.747–1.53.

Total plasma drug exposure (AUC_{0-inf}) was similar between subjects with ESRD dosed predialysis (3152 hours·pg/mL), postdialysis (3240 hours·pg/mL) and subjects with NRF (3802 hours·pg/mL). There was large intersubject variability in treprostinil AUC_{0-inf} value for each subject group ranging from 5%5 to 61%. The comparative box plot (Fig. 2) showed that AUC_{0-inf} of treprostinil was somewhat higher in NRF subjects than in ESRD subjects dosed postdialysis; however, 2 NRF subjects had much (2–4 fold) higher AUC_{0-inf} than the other 6 subjects (Fig. 2). The box plots also demonstrated that treprostinil AUC_{0-inf} in ESRD subjects were comparable when UT-15C SR was administered before and after dialysis. Statistical analysis (ANCOVA) showed that the GLSM ratio for AUC_{0-inf}, ESRD postdialysis versus NRF subjects was 0.771, with a 90% CI of 0.506–1.18.

The 90% CI for C_{max} and AUC_{0-inf} ratios (ESRD dosed postdialysis vs NRF) included 1.0, indicating that these treprostinil PK parameters of treprostinil were not statistically significantly different between the 2 subject groups. However, the 90% CIs were wide, primarily because of large intersubject variability and a small sample size. Based on GLSM ratios, treprostinil AUC_{0-inf} was about 23% lower and C_{max} was 7% higher in ESRD subjects with UT-15C SR dosed postdialysis when compared with subjects with NRF.

Safety Results

A complete list of adverse events (AEs) reported in this study is shown in Table 3. A total of 11 AEs in 5 (31%) subjects occurred during the course of the study. The most frequent AE was headache (n = 4; 25%) followed by nausea (n = 3; 19%). AEs were fairly evenly distributed in the subjects with NRF and subjects with ESRD; however, more subjects with NRF reported AEs after a single dose than the ESRD subjects. The timing of prostacyclin-related AEs (eg, headache, nausea) tended to occur around the individual

TABLE 3. Summary of Adverse Events by Treatment

Adverse Event	NRF Subjects (N = 8), n (%) [events]	ESRD Postdialysis (N = 8), n (%) [events]	ESRD Predialysis (N = 8), n (%) [events]	Total (N = 16), n (%) [events]
Any event	2 (25) [6]	2 (25) [2]	2 (25) [3]	5 (31) [11]
Headache	2 (25) [2]	2 (25) [2]	0 (0) [0]	4 (25) [4]
Nausea	1 (13) [1]	0 (0) [0]	2 (25) [2]	3 (19) [3]
Pain in jaw	1 (13) [1]	0 (0) [0]	0 (0) [0]	1 (6) [1]
Petechiae	1 (13) [1]	0 (0) [0]	0 (0) [0]	1 (6) [1]
Photophobia	1 (13) [1]	0 (0) [0]	0 (0) [0]	1 (6) [1]
Vomiting	0 (0) [0]	0 (0) [0]	1 (13) [1]	1 (6) [1]

patients C_{max}. All AEs, except one incidence of headache, were considered possibly or probably related to study drug. All AEs resolved by the end of the study without intervention. There were no significant changes in heart rate and blood pressure during the treatment period in either the NRF subjects or the subjects with ESRD.

DISCUSSION

The primary objective of this study was to assess the effect of renal impairment on the PK of treprostinil following oral administration of a 1 mg UT-15C SR tablet. Because treprostinil is extensively metabolized and urinary excretion is a minor elimination pathway for treprostinil, it is reasonable to carry out this study using the Reduced PK Study Design as recommended in the FDA Guidance. This design evaluated the ESRD subjects first and if substantial (50% or greater) changes in plasma exposure to treprostinil were observed, then further assessment would be carried out to determine the impact of mild or moderate renal impairment on treprostinil PK.

This study showed that mean plasma exposure to treprostinil in subjects with ESRD was about 23% lower than that in healthy subjects with NRF; this difference was not statistically significant, most likely because of a small sample size and large intersubject variability. Nevertheless, this extent of change (23% reduction) in overall plasma exposure to treprostinil in the most severe case of renal impairment (ie, ESRD subjects requiring dialysis) would not be clinically concerning, especially when the treprostinil diolamine dose is titrated to its desired pharmacological effect in patients. In addition, treprostinil C_{max} was not statistically different between the 2 subject groups, and the median C_{max} was comparable between ESRD subjects receiving the dose postdialysis and in healthy subjects with NRF. It would have been expected that severe renal impairment would have no effect on plasma treprostinil exposure. The mechanism for the slight reduction in treprostinil exposure in ESRD subjects observed in this study is not fully understood, perhaps owing to changes in patients' fluid status as these subjects were dosed after completion of dialysis, reduced oral bioavailability (ie, altered gastrointestinal physiology affecting absorption, increased first-pass metabolism), or was an artifact related to the small sample size and high intersubject variability.

As expected for drugs that undergo metabolism as the predominant elimination pathway, hemodialysis in the ESRD subjects (as assessed when subjects were dosed 4 hours before dialysis) did not seem to significantly remove treprostinil from the systemic circulation or alter the plasma profiles of treprostinil following administration of treprostinil diolamine tablet. Plasma exposure to treprostinil, AUCs, and C_{max} values were comparable in ESRD subjects dosed predialysis when compared with healthy subjects with NRF, especially taking into account of the large variability. A limitation of the study was the lack of genetic analysis of the CYP2C8 isoenzyme to exclude any patients with a genetic polymorphism of CYP2C8.

Overall, this study shows that treprostinil PKs following administration of a UT-15C SR tablet are not substantially altered in subjects with severe or end-stage renal impairment. Hemodialysis does not seem to contribute significantly to the elimination of treprostinil from the systemic circulation in ESRD subjects; and thus, treprostinil PKs in ESRD subjects were largely comparable with subjects with NRF regardless of the timing of the dose relative to hemodialysis.

The most frequent AEs (headache, nausea) were similar to those known to be prostacyclin related and have frequently been recorded during other clinical studies with treprostinil diolamine.

Treprostinil diolamine can be successfully dosed in patients with severe renal dysfunction and when they are on dialysis without the need for dose reduction or a modified dosing schedule. As treprostinil diolamine is a titratable drug, dosing should start at 0.125 or 0.25 mg twice a day with close observation to best treat the individual patient with an optimal dose based on clinical monitoring.

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