

RDEA594, A POTENT URAT1 INHIBITOR WITHOUT AFFECTING OTHER IMPORTANT RENAL TRANSPORTERS, OAT1 AND OAT3

L.-T. Yeh, Z. Shen, B. Kerr, *I. Tamai, V. Hingorani, V. Ong, T. Nguyen, M. Nguyen, B. Sheedy, K. Manhard, B. Quart
Ardea Biosciences, San Diego, United States, *Pharmacy, Kanazawa University, Kanazawa, Japan

Abstract

Background: RDEA594 has demonstrated serum uric acid (sUA) lowering effects in humans following dosing of either of RDEA594 or its parent, RDEA806, in over 200 healthy volunteers and patients. The lowering of sUA is directly linked to increased urinary excretion of uric acid. The increase of urinary uric acid excretion is believed to result from inhibition of the URAT1 transporter, which was responsible for uric acid re-absorption in the proximal tubule.

Objectives: Assessment of potential drug-drug interactions between RDEA594 and drugs whose elimination is dependent on other major renal transporters, primarily OAT1 and OAT3, was conducted in vitro, using oocytes or Fp293 cells, and in humans, by co-administration of the parent RDEA806 and Truvada (emtricitabine (FTC) 200 mg plus tenofovir disoproxil fumarate 300 mg). Elimination of tenofovir is known to be primarily through renal excretion dependent on OAT1 and to a lesser extent on OAT3.

Methods: OAT1 or OAT3 expressed oocytes or Fp293 cells were used to evaluate the uptake and inhibitory potential of RDEA594 upon those transporters. In man, a single-center, two-way cross-over, two-period, two-panel phase 1 study was conducted in 24 healthy adult subjects. In Panel 1, 800 mg RDEA806 was administered for 4-days to 12 subjects, and the effect of RDEA806 and RDEA594 on the pharmacokinetics (PK) of a single dose of Truvada was evaluated; in Panel 2, the effect of a 4-day course of Truvada on the PK of RDEA806 and RDEA594 was evaluated after an 800 mg single dose of RDEA806 in another group of 12 subjects.

Results: In vitro results indicated that RDEA594 is not a substrate of either OAT1 or OAT3, and is not an inhibitor of OAT1 and OAT3 at clinically relevant concentrations. RDEA806 and RDEA594 had no effect on the plasma PK of tenofovir or FTC. Comparing Truvada plus RDEA806/RDEA594 versus Truvada alone, the 90% confidence interval of the geometric mean ratio of C_{max} and AUC for both tenofovir and FTC fell within 80% to 125%, indicating an absence of interaction. The renal clearances of tenofovir and FTC were also found to be unaffected by concomitant RDEA806 treatment. Similarly, Truvada treatment was found to have no significant effect on the plasma PK of RDEA806 or RDEA594.

Adverse events were generally mild in severity and consistent with those frequently seen in Phase 1 studies

Introduction

Both RDEA594 and RDEA806 have been well tolerated in a total of over 300 subjects and patients. RDEA594 has demonstrated sUA lowering effects in humans following dosing of either RDEA594 or its parent, RDEA806. The lowering of sUA is directly linked to increased urinary excretion of uric acid, resulting from inhibition of the URAT1 transporter, which is responsible for uric acid re-absorption in the proximal tubule of the kidney.

Probenecid, a known uricosuric drug, also inhibits urate re-absorption. At an effective dose level, probenecid also inhibits renal elimination of many drugs such as acyclovir, allopurinol, cefotaxime, penicillins, cephalosporins, etc. Recent studies have indicated that probenecid is a potent inhibitor of renal organic transporters, OAT1 and OAT3, with K_i values lower than unbound plasma probenecid concentration.

The present *in vitro* and clinical studies assess the drug-drug interaction potential for RDEA594 to interact with drugs eliminated through OAT1 and OAT3 transporters. Emtricitabine and tenofovir, which are primarily excreted by the kidneys by a combination of glomerular filtration and active secretion, were used to evaluate the potential for interactions.

Methods

In Vitro Evaluation:

Uptake of RDEA594 was conducted in OAT1 or OAT3 expressing oocytes using p-aminohippurate (PAH) for hOAT1 and estrone 3 sulfate (E3S) for hOAT3 as positive controls. Uptake ratios were calculated as follows:

$$UR = U_{transporter} / U_{control}$$

Where:

- UR is the uptake ratio between transporter expressing and control oocytes
- $U_{transporter}$ is the mean rate of uptake into transporter expressing oocytes [pmol/oocyte/hr]
- $U_{control}$ is the mean rate of uptake into control oocytes [pmol/oocyte/hr]

Inhibition of RDEA594 was conducted in OAT1 or OAT3 expressing Fp293 cells using PAH as a hOAT1 substrate and E3S as the hOAT3 substrate

Clinical Evaluation: in healthy volunteers:

RDEA806-104 was an open-label, 2-way cross-over, 2-period, 2-panel study with a total of 24 healthy adult male and female subjects, 12 per panel. In Panel 1, 12 subjects received Treatment A as single dose of Truvada® (Gilead Sciences, Inc.; emtricitabine 200 mg plus tenofovir disoproxil fumarate 300 mg) alone and Treatment B as RDEA806 800 mg once daily (qd) on Days 1 to 4 and a single dose of Truvada on Day 2 in a crossover fashion with 6 subjects per treatment period. In Panel 2, 12 subjects received Treatment C as a single dose of RDEA806 800 mg on Day 2 and Treatment D as Truvada one tablet qd on Days 1 to 4 and a single dose of RDEA806 800 mg on Day 2 in a crossover fashion with 6 subjects per treatment period.

Pharmacokinetic (PK) assessments included analysis of RDEA806, RDEA594, emtricitabine and tenofovir in plasma and urine. Pharmacodynamic (PD) assessments included serum urate concentrations, urine urate concentrations, amount of uric acid recovered in the urine, and renal clearance of uric acid.

Results of In Vitro Evaluation

Table 1. In vitro, RDEA594 is a weak substrate of hOAT1 and hOAT3

RDEA594	Uptake Ratio vs. Control	
	hOAT1	hOAT3
Positive Control	81	13
5 μ M	2.6	2.0
25 μ M	1.3	1.4

Table 2. Clinically, RDEA594 free drug concentrations are not sufficient to inhibit OAT1 and OAT3; in contrast, clinical doses of probenecid produce concentrations significantly higher than its K_i

Compound	Dose (mg)	$C_{max, total}$ (μ M)	$C_{max, free}$ (μ M)	K_i (μ M)	
				OAT1	OAT3
RDEA594	200	13.7	0.27		
	600*	41.9	0.81	4.3	3.5
	500	124	13.6		
	1000	244	26.8		
Probenecid ^{1,2}	2000	521	57.3		

* Projected for current clinical formulation given with food

Results of Clinical Evaluation

Figure 1. Similar plasma time-concentration profiles of emtricitabine and tenofovir when administered alone or with RDEA806.

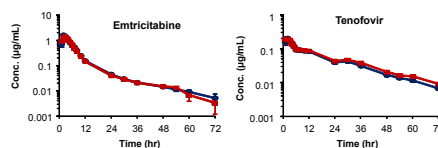


Figure 2. Similar urinary excretion of emtricitabine and tenofovir when administered alone or with RDEA806

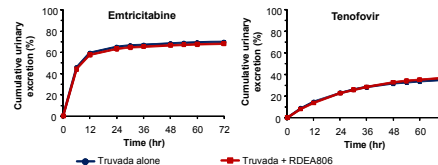


Table 2. Plasma PK and urinary excretion/clearance of emtricitabine and tenofovir were not affected in the presence of RDEA806 and RDEA594

Analyte	Parameter	Co-treatment	Geometric mean	Ratio*	CI90% [lower, upper]
Emtricitabine	AUC_{0-72h} (μ g hr/mL)	None	10.2	0.929	[0.889, 0.972]
		RDEA806	9.47		
	Ae_{0-72h} (mg)	None	139	0.974	[0.937, 1.01]
		RDEA806	136		
	CLr (L/hr)	None	13.7	1.05	[1.01, 1.09]
		RDEA806	14.3		
Tenofovir	AUC_{0-72h} (μ g hr/mL)	None	3.07	1.1	[1.05, 1.15]
		RDEA806	3.37		
	Ae_{0-72h} (mg)	None	47.2	1.05	[0.994, 1.12]
		RDEA806	49.7		
	CLr (L/hr)	None	15.4	0.959	[0.919, 1.00]
		RDEA806	14.8		

* Geometric mean ratio: emtricitabine/tenofovir+RDEA806 treatment vs. emtricitabine/tenofovir alone

Table 3. Plasma PK and urinary excretion/clearance of RDEA594 were not affected in the presence of emtricitabine and tenofovir

Compound	Co-treatment	Geometric mean	Ratio*	CI90% [lower, upper]	
RDEA594	AUC_{0-72h} (hr^{μ} ug/ml)	None	23.9	1.24	[1.01, 1.52]
		Truvada	29.7		
	Ae_{0-72h} (mg)	None	46.0	1.07	[0.837, 1.36]
		Truvada	49.1		
	CLr (L/hr)	None	1.93	0.860	[0.717, 1.03]
		Truvada	1.66		
RDEA806**	AUC_{0-72h} (hr^{μ} ug/ml)	None	16.4	1.16	[1.00, 1.34]
		Truvada	19.0		

* Geometric mean ratio: emtricitabine/tenofovir+RDEA806 treatment vs. RDEA806 alone

** There was only trace amount of RDEA806 excreted to urine; therefore, Ae and CLr for RDEA806 was not evaluated

Conclusions

- RDEA594 free-drug concentrations are not sufficient to inhibit OAT1 and OAT3; in contrast, therapeutic doses of probenecid produce concentrations significantly higher than its K_i for OAT1 and OAT3
- Clinical results demonstrate that RDEA806 and RDEA594 do not alter plasma concentrations or renal excretion of tenofovir or emtricitabine; two drugs known to be renally excreted and highly dependent on renal transporters
- Truvada co-administration did not significantly affect either RDEA806 or RDEA594 pharmacokinetics
- Unlike probenecid, which has significant drug-drug interaction liabilities through its effects on OAT1 and OAT3, RDEA594 appears to have minimal drug-drug interaction potential with these transporters
- Evaluation of potential drug-drug interactions of RDEA594 with other renal transporters is underway

References

- Takeda M.; Narikawa S.; Endou H., Characterization of organic anion transporter inhibitors using cells stably expressing human organic anion transporters. *Eur. J. Pharmacology* **2001**, 419, 113-120.
- Selen A.; Amidon G. L.; Welling P.G., Pharmacokinetics of probenecid following oral doses to human volunteers. *J. Pharm. Sci.* **1982**, 71 (11), 1238-1242.