

Abstract

Background: RDEA806 is a novel NNRTI with potent in vitro activity against both wild-type HIV ($EC_{50} = 3$ nM) and the majority of viruses resistant to the currently approved NNRTIs. Because HIV drugs are given in multi-drug "cocktails," we examined the potential for drug-drug interactions with RDEA806.

Methods: To evaluate the drug-drug interaction potential, in vitro and in vivo preclinical studies have been conducted to evaluate RDEA806 as an enzyme inhibitor or inducer, phenotyping of RDEA806 metabolism using cDNA-expressed cytochrome P450 enzymes (CYPs), inhibition of RDEA806 metabolism in pooled human liver microsomes with CYP-selective chemical inhibitors, co-administration of RDEA806 with ritonavir in rats, and co-administration of RDEA806 with ritonavir in healthy human volunteers.

Results: At projected therapeutic drug levels, RDEA806 should not be an inhibitor of CYP1A2, 2C19, or 2D6 (IC_{50} values greater than 100 μ M for these isoforms), nor should it be an important inhibitor of 2C9 or 3A4 (IC_{50} greater than 10.3 μ M for these isoforms). RDEA806 did not induce hepatic CYP3A, CYP1A, CYP2B, and CYP4A contents or activity in male rats following 8-day dosing up to 150 mg/kg. Phenotyping results indicated that Phase I metabolism of RDEA806 may involve multiple P450 isozymes, but no single enzyme was shown to play a predominant role. Following co-administration of 20 mg/kg RDEA806 with either 20 or 40 mg/kg ritonavir in rats, there were only modest increases in C_{max} and AUC of RDEA806. These increases were significantly lower than those observed with protease inhibitors co-administered with ritonavir (10 mg/kg) in rats (Kempf, et al.). A confirmatory, randomized, placebo-controlled, single-dose interaction study in healthy volunteers is currently underway.

Conclusions: Based on preclinical evaluations, RDEA806 appears to have limited potential for drug-drug interactions. The lack of a significant interaction with ritonavir is being confirmed in humans.

Introduction

RDEA806 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type-1 (HIV-1). For the NNRTIs, many mutations cause cross-resistance, especially the K103N mutant, rendering this class unavailable for combination therapies in NNRTI-naïve subjects infected with these resistant viruses. For NNRTI-naïve subjects without NNRTI resistance mutations at the beginning of treatment, the development of resistance leads to treatment failure and the loss of the entire class as a treatment option. The most widely prescribed NNRTI, efavirenz, is also associated with central nervous system side effects due to its brain penetration and has significant drug-interaction potential due to its ability to induce hepatic enzymes, as well as to inhibit cytochrome P450 isozymes 2C9, 2C19, and 3A4 (Sustiva® U.S. Package Insert, January 2007).

Although there are NNRTIs in development that are active against the NNRTI-resistant viruses, they have tolerability issues, such as rash, and significant drug-interaction potential. NNRTIs with activity against resistant virus, excellent tolerability and reduced potential for drug-interactions are urgently needed to expand the NNRTI armamentarium.

RDEA806 has the potential to meet these unmet medical needs:

- Preclinical testing has shown a better resistance profile of RDEA806 over currently marketed NNRTIs against multiple HIV reverse transcriptase mutations, including the most common mutation at position 103 (K103N) and the double mutation at 103 and 100 (K103N + L100), which decreases the activity of efavirenz by over 170-fold, and confers treatment resistance against the entire current class of NNRTIs.

- RDEA806 also has a much higher barrier to resistance than efavirenz; in parallel serologic studies with wild-type and K103N virus high level resistance to RDEA806 was not obtained for almost one year, compared to 3 months for efavirenz with wild-type virus and one month for K103N.

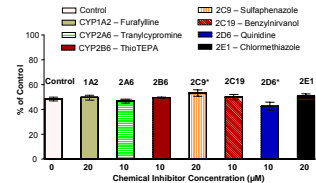
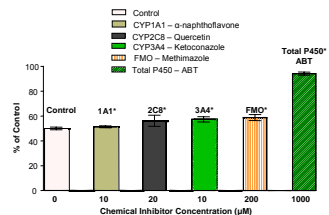
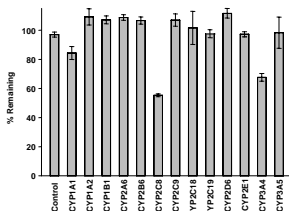
- In vitro testing demonstrated that RDEA806 is a weak inhibitor of CYP3A4 and an inducer of CYP3A4 only at higher doses, and the administration of RDEA806 with ritonavir did not significantly change the exposure and metabolism of RDEA806 in studies in rats and in healthy human volunteers.

Methods

The potential of RDEA806 to act as a direct or mechanism-based inhibitor of major cytochrome P450 (CYP) isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was evaluated in human liver microsomes (Table 1). Human liver microsomes were incubated with marker substrates in the presence (0.0305 to 200 μ M) or absence of RDEA806. The decreased rate of reaction with increased RDEA806 concentrations yielded estimated IC_{50} values of RDEA806. The effect of 14-day, daily oral administration of RDEA806 at 15, 50, and 150 mg/kg/day on CYP enzyme induction was evaluated in male rats (Table 2). For phenotyping, RDEA806 was incubated with cDNA-expressed isozymes, and the depletion of RDEA806 was monitored by high-performance liquid chromatography with tandem mass spectrometry. The recombinant CYPs used included CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, and 3A5. The results were further confirmed by incubating [¹⁴C]RDEA806 (2.75 μ M) with human liver microsomes (1 mg microsomal protein per mL) with or without specific chemical inhibitors, which included *o*-naphthoflavone (for CYP1A1), furafylline (for CYP1A2), tranylcypromine (for CYP2A6), thioTEPA (for CYP2B6), sulfaphenazole (for CYP2C9), quercetin (for CYP2C8), benzylnvanol (for CYP2C19), quinidine (for CYP2D6), chlormethiazole (for CYP2E1), ketoconazole (for CYP3A4), methimazole (for FMO), and amiofenbutazolidone (for total P450) (Figure 1). To study the PK profile of RDEA806

when co-administered with ritonavir, male Sprague-Dawley rats ($n = 4$ /dose group) were orally dosed with RDEA806 at 20 mg/kg with or without ritonavir (20 or 40 mg/kg). Ritonavir was dissolved in 20% EtOH/5% dextrose/30% PEG400/45% water with the addition of equivalent molar ratio of methyl sulfuric acid to ritonavir, and dosed at 0.5 hr prior to RDEA806 dosing. Plasma was collected pre dose (0 hr) and at 0.25, 0.5, 1, 3, 6, 12, and 24 hr following RDEA806 dosing (Table 3). In humans, a single-center, randomized, open-label study to assess the PK enhancement effects of low-dose ritonavir on 100 mg RDEA806 in 10 subjects was conducted. All subjects entered the clinic on Day -1 and were confined to the clinic for 4 days. Each subject received a single dose of 100 mg RDEA806 with a standard breakfast on Day 1, five of whom were also co-administered 100 mg ritonavir with RDEA806. Blood for PK assessments was collected through 72 hours post dose (Table 4).

Figure 1. Lack of Primary P450-Metabolizing Enzyme for RDEA806



* statistically significant difference (P < 0.05)

Results

Table 1. Weak Inhibitory Potential of RDEA806 to Major P450 Enzymes

Isozyme	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Substrate	phenacetin	diclofenac	S-mephenytoin	bufuralol	midozolam
IC_{50} (μ M)	> 100	14.4 (2.07)	> 100	> 100	32 (4.72)
					10.3 (2.7)

Table 2. No Effect on Body/Liver Weight and Enzyme Content/Activity of RDEA806 Following Multiple Dosing in Rats

Parameters	Relative Fold Changes from Control		
	15 mg/kg	50 mg/kg	150 mg/kg
Body Weight	0.97	1.04	1.06
Liver Weight	1.00	1.02	1.00
Liver/Body Weight Ratio	0.97	1.01	1.06
Total CYP Content	0.89	0.76	0.74
CYP 3A1/2 Contents	0.67	0.93	0.92
CYP 3A Activity	1.01	0.98	1.01
CYP 1A1 Activity	1.24	1.11	1.01
CYP 1A Content	0.94	0.98	1.10
CYP 2B1/2 Contents	1.15	1.18	1.18
CYP 2B Activity	0.92	1.26*	1.32*
CYP 4A1/3 Contents	1.34	1.09	1.23

Note: *dosing for 14 days; *dexamethasone dosing for 4 days; *no statistically significant difference (P > 0.05); nd = not detected

Table 3. Lack of Drug-Drug Interaction with Ritonavir Following Single Oral Dosing in Rats

Dose (mg/kg)	Ritonavir	RDEA806	C_{max} (μ g/mL)	$t_{1/2}$ (hr)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{0-24hr} (μ g·hr/mL)	$t_{1/2}$ (hr)
0	20	Mean	0.206	0.0029	5.25	24.0	2.51	2.91
		%CV	24.6	71.1	28.6	0.00	8.57	24.6
20	20	Mean	0.388	0.0019	1.81	24.0	3.96	2.55
		%CV	19.3	30.5	154	0.00	27.1	23.1
40	20	Mean	0.629	0.0161	1.88	24.0	6.85	3.47
		%CV	30.9	64.4	148	0.00	26.0	23.3
Ratio 20/20	Mean	1.88	0.655	NA	NA	1.58	NA	
		Ratio 40/20	Mean	3.05	5.55	NA	NA	2.73

Table 4. Ritonavir Did Not Alter RDEA806 Metabolism Following Single Oral Dosing in Healthy Volunteers

Dose (mg)	Ritonavir	RDEA806	C_{max} (μ g/mL)	T_{max} (hr)	AUC_{0-24hr} (μ g·hr/mL)	$t_{1/2}$ (hr)
0	100	Mean	0.181	5.60	0.747	8.02
		%CV	115	46.6	51.7	65.9
100	100	Mean	0.0857	11.2	1.13	6.49
		%CV	62.8	63.9	43.4	30.9
Ratio	Mean	0.473	NA	1.51	NA	

- At detected therapeutic drug levels, taking into account protein binding, RDEA806 should not be an inhibitor of CYP1A2, 2C9, 2C19, 2D6 or 3A4.
- In male rats, doses up to 150 mg/kg/day did not induce hepatic CYP3A, CYP1A, CYP2B and suggested little liability in enzyme induction.
- Using fresh human hepatocytes, RDEA806 had no effect on CYP1A2 activity and was only 21% as effective as rifampin at 10 μ M on CYP3A4 activity (data not shown).
- P450 reaction phenotyping indicated that the metabolism of RDEA806 may involve several P450 isozymes, but no one enzyme was shown to play a predominant role. The involvement of non-P450 enzymes could not be ruled out for RDEA806 metabolism.
- Co-administering with ritonavir did not significantly change the pharmacokinetics of RDEA806 based on AUC and $t_{1/2}$. The delayed T_{max} of RDEA806 when co-administered with ritonavir may be due to the formulation of ritonavir.

Conclusions

- Evaluation of the drug-drug interaction liability of RDEA806 at preclinical and clinical programs demonstrated that RDEA806 is likely to be an inducer or inhibitor of major P450 enzymes and be affected by CYP3A4 inhibitors.
- RDEA806 has less drug-drug interaction liability compared to current marketed NNRTIs.

References

1. Kempf, et al. (1997) Pharmacokinetic Enhancement of Inhibitors of the Human Immunodeficiency Virus Protease by Coadministration with Ritonavir. Antimicrob. Agents Chemother. 41: 654-660