

Ritonavir Increases Concentrations of the CXCR4 Antagonist AMD11070 in Healthy Volunteers

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Abstract

Background: Many HIV-infected patients either do not tolerate available antiretroviral drugs or develop virologic failure due to incomplete suppression of viral replication and development of antiviral resistance. Thus, the identification of new classes of antiretroviral drugs with unique mechanisms of action is an important goal of antiretroviral drug development. AMD070, a CXCR4 antagonist, inhibits the replication of HIV-1 *in vitro*. It is rapidly absorbed following oral administration and represents a new class of antiretroviral drug for the management of HIV infection. Since AMD070 is a substrate of CYP3A4 and P-glycoprotein and will be likely co-administered with ritonavir (RTV), we tested the hypothesis that co-administration of RTV favorably alters the pharmacokinetic (PK) profiles of AMD070.

Methods: 23 healthy male subjects were dosed with a single 200-mg AMD070 on Day 1. RTV (100 mg q12h) was dosed from Day 3 to Day 18. A single 200-mg AMD070 dose was given simultaneously with the first dose of RTV on Day 3 and with the morning dose of RTV on Day 17. Blood samples were collected for the determination of AMD070 concentration for 48 hr after each administration of AMD070 on Days 1, 3, and 17. Safety of AMD070 alone and during co-administration with RTV was also assessed. Non-compartmental PK analyses were performed with WinNonlin.

Results: 21 subjects completed the study and were included in the final PK analysis; two discontinued for reasons other than safety. All adverse events were \leq grade 2. AMD070 alone had the following pharmacokinetic features (geometric mean with 95% confidence interval): 2.9 (2.4-3.6) hours for time to peak blood concentration (T_{max}), 231 (163-329) ng/ml for peak concentration (C_{max}), 876 (701-1094) hr.ng/ml for 48-hour AUC (AUC₀₋₄₈), 16 (14-18) hours for terminal half-life (t_{1/2}), and 216 (173-270) L/hr for total body clearance (CL/F). The initial dose of RTV decreased T_{max} by (geometric mean ratio with 90% confidence interval) 29 (13-41) % and CL/F by 38 (22-50) % while increasing C_{max} by 39 (3-89) %, AUC₀₋₄₈ by 55 (24-94) % and t_{1/2} by 20 (0-43) %. RTV at steady-state decreased T_{max} by 25 (5-41) % and CL/F by 27 (7-43) % while increasing C_{max} by 47 (8-101) %, AUC₀₋₄₈ by 34 (4-72) % and t_{1/2} by 16 (1-34) %. **Conclusions:** AMD070 concentrations were increased with concomitant RTV dosed to steady state (14 days) in healthy volunteers.

Background

Despite the availability of many effective antiretroviral drugs, clinician's treatment options are still challenged by drug toxicities and the emergence of drug resistant HIV. The identification of a new class of drugs with a novel mechanism of action, durable efficacy, and lack of cross-resistance with existing antiretroviral drug classes remains a continuing therapeutic need.

AMD11070 belongs to a novel class of antiretroviral entry inhibitors. It is a specific and reversible antagonist of the CXCR4 chemokine receptor and has a potent and selective ability *in vitro* to inhibit X4 viral replication by blocking fusion and viral entry into the cell. The development of a previously studied CXCR4 inhibitor, AMD3100, as an antiretroviral drug was terminated due to poor oral bioavailability and adverse effects. AMD11070 is being developed as an orally available antiretroviral drug.

In the first-in-human phase I study of AMD11070, in which healthy volunteers received either a single dose or 7 doses twice daily, without a placebo control, the drug was well tolerated, well absorbed after oral dosing, and peaked in 1-2 hours. Multiple dosing suggests lack of dose proportionality and a terminal half-life of 11-16 hours. A majority of subjects dosed with 200 mg BID attained plasma concentrations at or near *in vitro* EC₅₀ 24 hours after dosing. AMD11070, like its predecessor AMD3100, showed a dose-response for leukocytosis which may serve as a surrogate marker for CXCR4 inhibition.

Ritonavir is both an inhibitor and inducer of CYP3A4 substrate drugs and is commonly dosed with other protease inhibitors to "boost" their plasma concentration through CYP 3A4 inhibition. Additionally, ritonavir inhibits p-glycoprotein which enhances the absorption and alters the distribution of substrate drugs.

AMD11070 is primarily cleared by metabolism with <1% of the oral dose appearing unchanged in the urine. *In vitro* studies using human liver microsomes have shown that AMD11070 is primarily metabolized by CYP3A4. It is also believed that AMD11070 is a substrate for P-GP. In rat studies, coadministration of RTV increased the AUC, C_{max}, and bioavailability of AMD11070 by 58%, 158%, and 66%, respectively. In dog studies, there was no significant increase in the AUC for AMD11070 when co-administered with either a single dose of RTV, or at RTV steady-state.

Because of the potential for a AMD11070 - ritonavir interaction, we performed this pharmacokinetic (PK) drug interaction study to assess the interactions of AMD11070 with ritonavir given both as a single dose and twice a day for 2 weeks.

Note: AMD11070 was recently placed on clinical hold by the FDA due to liver histology changes observed in longer term pre-clinical toxicity experiments. These findings are currently under investigation.

Objectives

- Determine the acute and steady-state effects of low-dose RTV on the pharmacokinetics of AMD11070 in healthy male volunteers
- Assess the safety of coadministration of low-dose RTV with AMD11070

Methods

Study Site:

Academic medical centers (Johns Hopkins University and University of Washington), General Clinical Research Center

Study Population:

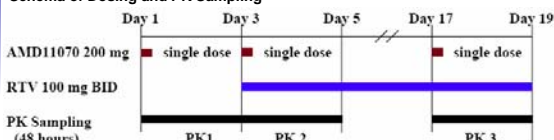
Twenty-three adult healthy men with no active medical illness by history, physical, or laboratory evaluation

Study Design

- Phase 1, open label, inpatient PK drug-drug interaction study
- Day 1:
 - AMD11070 200 mg p.o. single dose
 - PK1 sampling: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 34, 48 hours post dose
- Day 3:
 - AMD11070 200 mg p.o. single dose
 - Ritonavir 100 mg p.o. BID (Day 3 – 16)
 - PK2 sampling: through 48 hours as above (Day 3-4)
- Day 17:
 - AMD11070 200 mg p.o. single dose
 - Ritonavir 100 mg p.o. BID continues (Day 17 – 18)
 - PK3 sampling: through 48 hours as above (Day 17-18)

Daily safety and clinical evaluation; laboratory monitoring of hematology, chemistry and hepatic toxicity and function and trough AMD11070 were done on the pre-specified days during the hospital stay.

Schema of Dosing and PK Sampling



Data Analysis

- Non-compartmental pharmacokinetic analysis was used to estimate the area under the concentration-time curve (AUC), peak concentration (C_{max}), time to maximum concentration (T_{max}), terminal elimination half-life (t_{1/2}), clearance (CL/F), and volume of distribution (V/F) for AMD11070 and ritonavir.
- Geometric mean ratios (with 90% confidence intervals) of PK parameters were calculated for AMD11070 for acute (PK2/PK1) and for steady-state (PK3/PK1) RTV interaction to evaluate the magnitude of drug interactions.

Results

- Demographics: 57% African-American; 43% Caucasian; median age 42 (range: 18 - 53)
- All subjects tolerated the study drugs well. Reversible, mild to moderate grade adverse effects were seen in 4 subjects (23%) on AMD11070 alone in a 2 day period and in 16 subjects (70%) when taking AMD11070+RTV over a longer 16 day period (Table 1).
- There were no grade 3 or 4 related adverse events or findings of hepatotoxicity.
- Leukocytosis was measurable in all subjects.

Table 1. Summary of Safety Data.

Adverse Event	AMD11070 Alone		AMD11070 + Ritonavir	
	Period 1 (Day 1-2)		Period 2 (Day 3-18)	
	Grade 1	Grade 2	Grade 1	Grade 2
Diarrhea	1	1	8	
Lower abdominal			6	
Upper abdominal			5	
Headache	2	1	3	3
Other symptoms	3	0	17	2
Lipase elevation			1	1
Hypoglycemia				1
CPK elevation			1	

Figure 1. AMD11070 concentration (log scale) vs. time profile for all PK sampling periods. In the presence of ritonavir, both with a single dose or 14 days dosing, concentrations of AMD11070 are higher at nearly all time points.

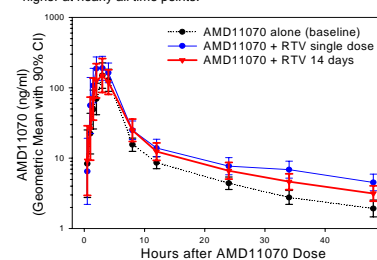
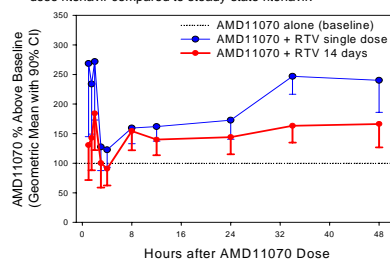


Table 2. Geometric mean ratio (90% confidence interval) PK3 / PK1 (RTV steady-state +AMD11070 versus AMD11070 alone) and PK2 / PK1 (RTV single dose + AMD11070 versus AMD11070 alone). AMD11070 data is all single dose data over a 48 hour PK period.

Parameter	Acute RTV Day 3 v Day 1	Steady-State RTV Day 17 v Day 1
AUC ₀₋₄₈	1.55 (1.24 - 1.94)	1.34 (1.04 - 1.72)
C _{max}	1.39 (1.03 - 1.89)	1.47 (1.08 - 2.01)
T _{max}	0.71 (0.59 - 0.87)	0.75 (0.59 - 0.95)
t _{1/2}	1.20 (1.00 - 1.43)	1.16 (1.01 - 1.34)
CL/F	0.62 (0.50 - 0.78)	0.73 (0.57 - 0.93)
V/F	0.75 (0.57 - 0.99)	0.85 (0.63 - 1.14)

Figure 2. Concentration (log scale) change from AMD 11070 alone at the corresponding sampling time point. The magnitude of relative changes is greatest immediately after dosing and during the terminal elimination. The differences appear larger for single dose ritonavir compared to steady-state ritonavir.



Conclusion

- Ritonavir caused a statistically significant, but modest, increase in the AMD11070 exposure, roughly 40-50% increase in C_{max} and AUC, during both the acute and steady-state phases of the study. The initial increase with the first ritonavir dose was largely sustained with continued dosing of ritonavir.
- The increase in exposure was associated with decreases in CL/F and V/F, with slightly smaller changes in half-life; this suggests that the mechanism of the increased concentration may have been a combination of inhibition of metabolism and increase in bioavailability, possibly as a result of CYP3A4 and p-glycoprotein inhibition by ritonavir.
- The increased concentrations of AMD11070 due to concomitant ritonavir dosing may result in clinically beneficial antiviral effects or detrimental effects due to side effects; however, the magnitude of the change is small and would likely only be clinically significant if AMD11070 has a narrow therapeutic window. Accordingly, dose adjustments are not clearly needed based on this data.

