Atazanavir Modestly Increases Plasma Levels of Raltegravir in Healthy Subjects

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Raltegravir is an HIV integrase inhibitor that is metabolized through glucuronidation by uridine diphosphate glucuronosyltransferase 1A1, and its use is anticipated in combination with atazanavir (a uridine diphosphate glucuronosyltransferase 1A1 inhibitor). Two pharmacokinetic studies of healthy subjects assessed the effect of multiple-dose atazanavir or atazanavir-boosted atazanavir on raltegravir levels in plasma. Atazanavir and atazanavir plus ritonavir modestly increase plasma levels of raltegravir.

Raltegravir is a novel antiretroviral agent that targets HIV integrase, the enzyme that catalyzes the process that results in integration of HIV DNA into the genome of the host cell [1]. Raltegravir has demonstrated potent in vitro activity and robust clinical activity in treatment-naive and treatment-experienced patients [2–6]. Raltegravir is indicated to be administered in combination with other anti-HIV drugs, such as atazanavir.

Atazanavir is a protease inhibitor that is metabolized by the cytochrome P450 system (predominantly by cytochrome P450 3A), and it is an inhibitor of both cytochrome P450 3A and uridine diphosphate glucuronosyltransferase (UGT) 1A1 at clinically relevant concentrations [7, 8]. For treatment-experienced patients, atazanavir is recommended in combination with ritonavir, a known inhibitor of cytochrome P450 3A that increases atazanavir plasma levels [9]. In addition to inhibiting some drug-metabolizing enzymes, ritonavir induces others, including glucuronosyltransferases [9].

Raltegravir is metabolized predominantly through glucuronidation by UGT1A1 [10]. In contrast with atazanavir and ritonavir, raltegravir does not appear to be an inducer or inhibitor of enzymes involved in drug metabolism [11]. On the basis of the potential for both atazanavir and ritonavir to affect the pharmacokinetics of raltegravir, a pharmacokinetic investigation of this combination was warranted. Ritonavir alone has been shown to have no clinically meaningful effect on raltegravir pharmacokinetics [12]. This report describes 2 raltegravir interaction studies involving healthy subjects, 1 of which used atazanavir alone and 1 of which used atazanavir in combination with ritonavir, investigating the effect of atazanavir alone and atazanavir plus boosting doses of ritonavir on raltegravir pharmacokinetics. The effect of raltegravir on atazanavir pharmacokinetics was not investigated because of the low likelihood of a clinically meaningful interaction [11].

Methods. Study I was a double-blind, randomized, placebo-controlled, 2-period study involving 12 young, healthy, male subjects that was designed to study the interaction between raltegravir and atazanavir. In period 1, subjects received 100-mg raltegravir (n = 10) or placebo (n = 2). Although the recommended therapeutic dose of raltegravir is 400 mg, a 100-mg dose was used in this initial atazanavir interaction study. Because the degree of the inhibitory effects of atazanavir on the pharmacokinetics of raltegravir was unknown, a lower dose of raltegravir was selected to preserve a wide safety margin in the case of a major adverse effect.

There was a 4-day washout between period 1 and period 2. In period 2, subjects received 400-mg atazanavir once daily for 9 days. On day 7, subjects received 100-mg raltegravir or placebo, in conjunction with atazanavir. Atazanavir was administered open-label, and raltegravir administration was double-blind.

Study II was an open-label, sequential, 2-period study involving 10 young, healthy, male or female subjects that was designed to study the interaction between raltegravir and atazanavir plus ritonavir. In period 1, 400-mg raltegravir was administered every 12 h for 4 days. A dose of 400 mg was selected in this study, because this was anticipated to be the recommended therapeutic dose, and data from study I established the range of anticipated exposures at 400 mg to be within previously defined safety margins. In period 2, subjects received 400-mg raltegravir every 12 h with 300-mg atazanavir and 100-mg ritonavir once daily for 10 days.

In both studies, multiple doses of atazanavir or atazanavir plus ritonavir were administered to achieve steady-state levels...
of affected drug metabolizing enzymes, although a single-dose of raltegravir was administered in study I and multiple-doses were used in study II. Although multiple-dose administration is representative of clinical dosing, single-dose administration is appropriate for assessment of drug interactions with raltegravir, because raltegravir single-dose pharmacokinetics are predictive of multiple-dose behavior [13, 14].

To conduct pharmacokinetic assessments, plasma samples were collected and analyzed for raltegravir concentrations; full profiles were obtained for samples collected on day 1 of period 1 and day 7 of period 2 for study I and on day 4 of period 1 and day 10 of period 2 for study II. The analytical method for the determination of raltegravir levels in human plasma has been described elsewhere [15]. Additional details regarding pharmacokinetic assessment can be found in the Appendix (online only). Geometric mean ratios and 90% CIs for raltegravir concentration at 12 h, maximum concentration, and area-under-curve values were constructed using an appropriate mixed-effects linear model applied to the log-transformed data.

Results. For study I, a total of 12 male subjects with a mean age of 35 years (range, 25–43 years) were enrolled; subjects weighed within 40% of their ideal body weight and had a mean weight of 75.3 kg (range, 64.0–87.0 kg). All of the enrolled subjects were Hispanic. In study II, a total of 10 healthy male (n = 9) and female (n = 1) subjects with a mean age of 39 years (range, 24–50 years) were enrolled; subjects weighed within 40% of their ideal body weight and had a mean weight of 84.7 kg (range, 55.4–105.7 kg). Seven of the 10 subjects were white, 1 was black, 1 was Hispanic, and 1 was multiracial. In both studies, all subjects were not infected with HIV and were in good general health.

The plasma raltegravir concentration profiles and the principal raltegravir pharmacokinetic parameters are summarized in figure 1 and table 1. Raltegravir administered in combination with atazanavir and in combination with atazanavir plus ritonavir was generally well tolerated. There were no serious adverse effects reported. No subject discontinued the studies because of adverse effects. There were no clinically meaningful electrocardiogram findings. In study I, 9 subjects reported 12 adverse events; 1 of these subjects was in the placebo group, and 8 of the events were determined to be related to the study drug. In study II, 10 subjects reported 40 adverse events, 25 of which were judged to be related to study drug. In both studies, elevation in total serum bilirubin levels was the most commonly reported adverse event, reported in 15 subjects after the initiation of atazanavir administration. Hyperbiliurubinemia is a known adverse effect of atazanavir [7]. All adverse events reported were transient and were rated mild to moderate in intensity.

Discussion. Data from both studies indicate that atazanavir alone or in combination with ritonavir increases the plasma concentration of raltegravir. The finding is attributed to the known inhibitive effect of atazanavir on UGT1A1 [8], the primary isozyme responsible for the metabolism of raltegravir.

The overall pharmacokinetic effect of atazanavir is similar in both studies, regardless of the addition of ritonavir, which has potential inductive properties on glucuronosyltransferases. In a direct comparison of mean raltegravir values, the effect of atazanavir alone showed a trend towards a slightly larger effect. The doses of atazanavir in the 2 studies differed, and the atazanavir (300 mg) boosted with ritonavir (100 mg) was projected to produce higher plasma concentrations in subjects, compared with concentrations produced by 400-mg atazanavir alone [7]. The clinical exposure-response relationship of atazanavir inhibition of UGT1A1 is unknown; however, the difference in inhibition potential of atazanavir in these 2 studies is not likely to be significant. The addition of ritonavir in study II may have resulted in a minor inductive effect, causing the slight trend towards a smaller effect.
The dose of raltegravir differed in the 2 studies, with the 400-mg recommended therapeutic dose administered in Study II and a lower 100-mg dose administered in Study I. The inhibitory effect of atazanavir was assessed in both studies by comparison with the same dose of raltegravir used in the control subjects. In that the pharmacokinetics of raltegravir are dose-proportional across the 100-mg to 800-mg dose range with no evidence of dose-dependent metabolism or clearance [13], the degree of this effect can be bridged to other doses of raltegravir. Additionally, the effect of atazanavir on raltegravir was similar in both studies, suggesting that such comparisons can be made using different doses of raltegravir.

The increase in plasma levels of raltegravir with atazanavir coadministration is modest and is not likely to be clinically meaningful. Raltegravir is an agent in a new class of antiretrovirals, and presently there exists no strong association of raltegravir pharmacokinetic summary measures with efficacy parameters to define the target pharmacokinetic parameter. For other classes of retroviral agents, there is a reasonable, but imperfect, association of efficacy with doses that achieve trough concentration values that exceed the protein adjusted 95% in-...


