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Drug Interactions

Exposure-related effects of unboosted atazanavir on the pharmacokinetics of raltegravir in HIV-1 infected patients

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Introduction: Raltegravir (RAL) is the first of a new class of antiretroviral drugs (integrase inhibitors), recently approved for first-line treatment in HIV-1 infected patients. This drug is primarily metabolized by glucuronidation mediated by the uridine diphosphate glucuronosyl transferase 1A1 isoenzyme (UGT1A1). Atazanavir (ATV), a strong inhibitor of UGT1A1, has shown to increase plasma levels of RAL approximately by 50% in healthy volunteers. The extent of such interaction has not been extensively studied in HIV infected patients.

Materials & Methods: A steady-state 12h intensive pharmacokinetic study was carried out in HIV-infected adults (>18 years) treated with a dual regimen of RAL 400 mg BID plus ATV 300 mg BID. RAL and ATV concentrations in plasma samples were determined by a validated LC-MS/MS method. In order to assess the RAL plasma increase via ATV inhibition of UGT1A1, PK parameters in our patients were compared with the ones from HIV-infected historical controls on 10-day RAL monotherapy. The AUCs for both drugs were estimated by the trapezoidal rule, correlations were performed by linear regression plot and comparison between groups by unpaired T-test or Mann-Whitney, as deemed appropriate.

Results: A total of 22 HIV-1 infected patients completed the study. Mean (±SD) age was 45 (±7) years, 19 were Caucasians and 17 male. Mean Body Mass Index (±SD) was 24 (±5) kg/m². Two patients had RAL AUC0-12 >35000 ng•h/mL and they were excluded from the analysis. RAL geometric mean (GM) AUC0-12 (90% CI) was 6166 (2772-15615) ng•h/mL and was comparable to historical HIV controls, whose GM AUC was 6851 (3667-12835) ng•h/mL. However, ATV exposure showed a high variability [GM AUC0-12 (90% CI) = 14622 (4052-45707) ng•h/mL with CV = 68.3 %]. Linear regression analysis showed a highly significant correlation between RAL and ATV AUC0-12 (r=0.600, p=0.005) and patients with ATV AUC0-12 >14622 ng•h/mL had a 2-fold higher exposure to RAL compared with patients with lower values [RAL GM AUC0-12 (90% CI): 8738 (3921-16060) vs 4027 (1823-12172) ng•h/mL, p=0.021]. A similar trend (despite a larger distribution) was observed using RAL and ATV trough concentrations [r= 0.452, p= 0.039 for linear regression; RAL GM Ctrough (90% CI): 235 (47-876) vs 440 (113-1290) ng/mL, p=0.112].

Conclusions: Overall, concomitant administration of unboosted ATV did not significantly increase RAL exposure. However, a wide inter-patient variability was observed for both drugs and the patients with higher ATV exposure had higher RAL plasma levels, confirming the expected booster effect.

No conflict of interest