Pharmacokinetics of dolutegravir and darunavir qd in HIV-infected patients: The DUALIS study.

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BACKGROUND

With successful antiretroviral therapy (ART) life-expectancy of HIV-patients has substantially increased, but ART-related long-term toxicities have led to the emergence of novel treatment strategies. The combination of the integrase inhibitor dolutegravir (DTG) and the ritonavir-boosted protease inhibitor darunavir (DRV/r) may play a key role in this setting. However, pharmacokinetic (PK) data is sparse to date.

METHODS

Pharmacokinetic (PK) sub-study of the prospective, randomized, non-blinded DUALIS study (Eudra-CT: 2015-000360-34). Virologically suppressed HIV-infected patients under ART were randomized and either kept on DRV/r plus NRTI backbone or switched to DTG 50 mg qd in combination with DRV/r 800/100 mg qd. Samples for PK analysis were obtained 4 weeks after switch (before and 1, 2, 4, 8 and 12 hours after intake of DTG plus DRV/r with food). Plasma levels of DTG and DRV were determined using HPLC.

RESULTS

A total of 10 patients (pts) (7 male, 3 female) with a median (IQR) age of 46 (37-50) years, a Body Mass Index of 24.6 (23.2-25.2), HIV RNA of 39 (19-44) cps/ml and a CD4-count of 715 (450-860) /µL were included in the sub-study. HIV RNA remained <50 cps/mL in all patients; 9/10 pts had detectable plasma levels prior to intake (C_{throat}). Median (IQR) C_{throat} levels were 637 (483-923) ng/mL for DTG and 1245 (575-1818) ng/mL for DRV. Maximum levels measured were 3427 (2964-4048) ng/mL for DTG and 6170 (5708-8950) ng/mL for DRV (figure 1). C_{throat} remained 4-17-fold above the protein-adjusted IC_{90} (64 ng/mL) for DTG and 1-22-fold above the protein-adjusted EC_{90} (200 ng/mL) for DRV (excluding the patient with undetectable DTG and DRV C_{throat} levels), respectively. Median (IQR) AUC_{12h} for DTG was 26,809 (22,441-28,459) ng/h/mL and for DRV 49920 (36,729-56,234) ng/h/mL, respectively. No drug-related adverse events (AEs) or serious AEs (SAEs) have been observed.

DISCUSSION

Overall drug levels showed an appropriate increase in DTG and DRV plasma levels after ART intake with C_{throat} levels for DTG and DRV above the protein-adjusted IC_{90} and EC_{90} levels, respectively, without evidence of virologic failure. Switching to once-daily dual therapy with dolutegravir in combination with ritonavir-boosted darunavir appears to be safe and effective with regard to their pharmacokinetic profiles.

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Figure 1:
Dolutegravir (DTG) and Darunavir (DRV) plasma levels (ng/mL) before and 1, 2, 4, 8 and 12 hours after intake.

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