High Concentration of Raltegravir in Semen of HIV-Infected Men: Results from a Substudy of the EASIER-ANRS 138 Trial

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Raltegravir concentrations and human immunodeficiency virus type 1 (HIV-1) RNA levels in semen samples from 10 treatment-experienced HIV-1-infected patients were measured after 24 weeks of raltegravir-based highly active antiretroviral therapy (HAART). Semen and plasma HIV-1 RNA levels were below 100 copies/ml and 50 copies/ml, respectively, in all samples. The median raltegravir concentrations in semen samples (n = 10) and in plasma samples (n = 9) drawn simultaneously were 345 (range, 83 to 707) ng/ml and 206 (range, 106 to 986) ng/ml, respectively. The median semen-to-plasma ratio of raltegravir concentration was 1.42 (range, 0.52 to 6.66), indicating good although variable levels of drug penetration of raltegravir in the seminal compartment.

Raltegravir is the first approved human immunodeficiency virus type 1 (HIV-1) integrase inhibitor which demonstrated potent antiviral efficacy in plasma samples from both treatment-experienced and treatment-naive HIV-infected patients (3, 11, 17). The male genital tract, however, represents a separate compartment, or “sanctuary site,” in which viral replication may persist in patients receiving combination antiretroviral therapy, despite a complete inhibition of HIV replication in blood (10, 15, 16, 18). HIV present in seminal plasma is responsible for sexual transmission of the virus, and an antiretroviral drug concentration within the male genital tract is therefore a potentially important factor affecting HIV replication and its sexual transmission (10, 18). No data are yet available on penetration of raltegravir in semen. Our aim was to assess the concentrations of raltegravir in seminal fluid and blood samples from 10 HIV-infected males enrolled in the EASIER-ANRS 138 trial.

EASIER-ANRS 138 is an open-label, multicenter, randomized clinical trial that demonstrated the noninferior antiviral efficacy at 24 weeks of a switch from enfuvirtide to raltegravir among treatment-experienced patients, with suppression of plasma HIV-1 RNA levels below 400 copies/ml under an enfuvirtide-based regimen (4). Ten male patients already enrolled in the EASIER-ANRS 138 trial gave written informed consent to participate in this semen substudy. Plasma and semen samples were collected after 24 weeks of raltegravir treatment (400 mg twice a day) given in combination with other antiretroviral drugs, so that steady-state conditions were ensured. Plasma samples were collected 5 h after the morning intake of raltegravir. Single semen samples were obtained at the same time by masturbation after a recommended 3-day period of sexual abstinence. All samples were rapidly centrifuged, and blood and seminal plasmas were stored at −80°C until analysis. The measures of HIV-1 RNA levels in blood and semen were performed with an adapted Cobas AmpliPrep/Cobas TaqMan HIV-1 assay (Roche, Meylan, France), with lower limits of detection of 50 and 100 copies/ml in plasma and semen, respectively (12). Raltegravir in plasma and semen was assayed by using validated liquid chromatography assays coupled with UV (320 nm) or mass tandem detection after liquid/liquid extraction (buffered plasma, pH 4, and dichloromethane/hexane extraction) and protein precipitation, respectively (7, 22). The limits of quantification of the assay were 10 ng/ml and 2.5 ng/ml in plasma and semen, respectively. The coefficients of variation of intra- and interassay precision and accuracy were below 15%. All results are presented as median (range).

The median age of the patients was 46.4 (range, 39.7 to 49.3) years, and their median CD4 cell count was 373 (range, 241 to 551) cells/mm3. In addition to raltegravir, 9 patients received a ritonavir-boosted protease inhibitor (PI) (darunavir for 5 patients, tipranavir for 2 patients, lopinavir for 1 patient, and a combination of lopinavir and fosamprenavir for 1 patient), 6 patients received 2 nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) (abacavir for 1 patient, tenofovir for 4 patients, emtricitabine for 2 patients, lamivudine for 3 patients, stavudine for 1 patient, and didanosine for 1 patient), 2 patients received 3 NRTIs (abacavir-tenofovir-emtricitabine), and 1 patient received didanosine-abacavir-tenofovir-exafirenaz. Raltegravir concentrations in plasma and semen samples obtained simultaneously at 5 h following drug intake on week 24 of treatment are shown in Fig. 1. A wide interpatient variability was observed for both compartments. Of note, raltegra-
medians of 345 (range, 83 to 707) ng/ml for semen samples.

Vir was detected in all seminal plasma samples analyzed, with

rations. The ratio is not calculated for patient 8.

A plasma sample from patient 8 was drawn at 9 h postdosing (hatched bars) and plasma (black bars) samples were drawn at 5 h postdosing. ANRS 138 trial at week 24, 5 hours following drug intake. Semen (grey samples obtained from 10 HIV-infected patients enrolled in the EASIER-938 BARAU ET AL. ANTIMICROB. AGENTS CHEMOTHER. treatments in quantitative methods to better understand a complex peripheral compartment. Clin. Pharmacol. Ther. 83:401–412.


References


