Seminal pharmacokinetics and antiviral efficacy of once-daily maraviroc plus lopinavir/ritonavir in HIV-infected patients

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Sir,

Sexual transmission of HIV-1 is currently the major way of viral spread worldwide: the quantification of seminal HIV-1 RNA has been clearly linked to the risk of transmission.1 The use of highly active antiretroviral treatment, besides providing immunovirological benefits, has been associated with viral control in the genital compartment of males and females. Nevertheless, occasional HIV-1 shedding has been demonstrated despite effective systemic therapy: insufficient penetration of antiretrovirals has been advocated as one of the reasons for HIV-1 compartmentalization.2 Although dual therapy and monotherapy have been advocated as one of the reasons for HIV-1 compartmental therapy: insufficient penetration of antiretrovirals has been associated with viral control in the genital compartment of males and females. Nevertheless, occasional HIV-1 shedding has been demonstrated despite effective systemic therapy: insufficient penetration of antiretrovirals has been advocated as one of the reasons for HIV-1 compartmentalization.2

This is the first report of maraviroc pharmacokinetics in seminal plasma when dosed at 150 mg once daily with a boosted protease inhibitor. Maraviroc accumulated in seminal plasma and compartmental maraviroc concentrations were found to be adequate and well above the protein-free 90% inhibitory concentration (IC90) (0.5 ng/mL) in all included subjects.

Lopinavir and ritonavir exposures in seminal plasma were similar to previous reports. In previous studies, maraviroc administered twice daily (150, 300 or 600 mg)10 showed median seminal concentrations between 80 and 804 ng/mL, being 89%–970% of plasma levels with a large interpatient variability (seminal levels ranging from 15.8 to 4920 ng/mL). Interestingly, in our patients both plasma and seminal maraviroc exposure were comparable to the values previously reported for maraviroc by the San Raffaele Scientific Institute Ethics Committee, Milan, Italy. Blood plasma and seminal plasma levels were measured by a validated ultraperformance liquid chromatography coupled with triple-quadrupole mass spectrometry method with a limit of detection of 0.125 ng/mL. Plasma HIV RNA was measured through a kinetic PCR molecular system (kPCR) (Versant HIV-1 RNA kPCR 1.0, Siemens Diagnostics) with a limit of quantification of 37 copies/mL. Seminal plasma HIV RNA was measured through an NASBATM-based real-time amplification using NucliSENS EasyQ® HIV-1 v2.0 (with a detection rate of 79% at 500 copies/mL).6 Mann–Whitney and χ² tests were used to test differences between variables while Spearman’s ρ was used to quantify the significance of correlations. Data are expressed as medians (IQRs); coefficient of variation (CV) was calculated as standard deviation/average.

Ten male patients were enrolled (aged 39.6 years (34.3–45.8)) and with a body mass index of 23.5 kg/m² (22.2–29.4). All patients had HIV RNA <37 copies/mL and the CD4 cell count was 619 cells/mm³ (547–683). Plasma and seminal samples were collected 11.6 (10.1–12.6) h and 9.2 (8–11.5) h after maraviroc intake, respectively. Maraviroc plasma and seminal concentrations were 223 ng/mL (103.9–312, CV 55.4%) and 527 ng/mL (234–852, CV 89.8%), respectively. The maraviroc seminal plasma-to-plasma ratio (ratioSP-P) was 291.6% (103.9%–405.1%, CV 80.5%) (Figure 1). Lopinavir plasma and seminal concentrations were 7935 ng/mL (6269–8958) and 233 ng/mL (136–803), respectively. The lopinavir ratioSP-P was 3.4% (2.6%–11.7%). Ritonavir plasma and seminal concentrations were 275 ng/mL (224–773) and 21 ng/mL (7–31), respectively. The ritonavir ratioSP-P was 8.3% (4.6%–10.7%).

The included patients were compared with five male patients in the control arm (receiving tenofovir/emtricitabine plus lopinavir/ritonavir), who were aged 43 years (37.3–44), had a body mass index of 22.3 kg/m² (21.5–24.8) and had a CD4 cell count of 480 cells/mm³ (449–531). Lopinavir plasma and seminal concentrations and ratioSP-P were 11521 ng/mL (10111–14018), 517 ng/mL (461–634) and 6.3% (3.3%–6.6%), respectively. Ritonavir plasma and seminal concentrations and ratioSP-P were 436 ng/mL (424–900), 18 ng/mL (16–35) and 6.2% (1.3%–8.1%), respectively. While RNA amplification was not effective in two samples, seminal HIV RNA was undetectable in all others (n=13).

The primary aim of this study was to describe the seminal pharmacokinetics of maraviroc (150 mg once daily) when given in association with lopinavir/ritonavir. The secondary objective was to analyse seminal HIV-1 replication in patients receiving this dual regimen.

Adult male patients enrolled in the VEMAN protocol6 were eligible for this substudy. The main inclusion criteria were no concomitant systemic or genital illness, a confirmed viral load <37 copies/mL, to be on protocol between weeks 48 and 96 and no coadministration of potentially interacting drugs. A written informed consent was signed by each participant after approval by the San Raffaele Scientific Institute Ethics Committee, Milan, Italy. Blood plasma and seminal plasma levels were measured by a validated ultraperformance liquid chromatography coupled with triple-quadrupole mass spectrometry method with a limit of detection of 0.125 ng/mL. Plasma HIV RNA was measured through a kinetic PCR molecular system (kPCR) (Versant HIV-1 RNA kPCR 1.0, Siemens Diagnostics) with a limit of quantification of 37 copies/mL. Seminal plasma HIV RNA was measured through an NASBATM-based real-time amplification using NucliSENS EasyQ® HIV-1 v2.0 (with a detection rate of 79% at 500 copies/mL).6
at double dosing (150 mg twice daily) with darunavir/ritonavir. This finding further supports the pharmacological suitability of once-daily dosing of 150 mg of maraviroc with lopinavir/ritonavir. Moreover, pharmacological findings were consistent with virological data: both in patients in the experimental dual-regimen arm and in the triple-drug arm, seminal plasma HIV RNA was undetectable. These data support the seminal virological effectiveness of the once-daily maraviroc plus lopinavir/ritonavir association and confirm, in general terms, the results of previous data on protease inhibitor-based dual regimens in the male genital tract.3

In conclusion, once-daily maraviroc at 150 mg administered with lopinavir/ritonavir showed adequate seminal exposure and full antiviral activity in the male genital tract.

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**References**