Switch from Enfuvirtide to Raltegravir Lowers Plasma Concentrations of Darunavir and Tipranavir: a Pharmacokinetic Substudy of the EASIER-ANRS 138 Trial

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We compared tipranavir and darunavir concentrations measured at steady state in 20 human immunodeficiency virus (HIV)-infected patients enrolled in the EASIER-ANRS 138 clinical trial who switched from enfuvirtide to raltegravir while maintaining the same background regimen. The geometric mean ratios of the observed predose concentration (C₀), maximum concentration of drug observed in plasma (Cₘₐₓ), and area under the plasma concentration-time curve (AUC) before (day 0) and after (week 24) the switch were 0.49, 0.76, and 0.67 and 0.82, 0.68, and 0.64 for tipranavir and darunavir, respectively. The virologic consequences of these drug interactions have yet to be determined.

Among patients with multidrug-resistant human immunodeficiency virus type 1 (HIV-1) infection, salvage antiretroviral regimens, including enfuvirtide, have demonstrated sustained efficacy. Nowadays, reluctance to use subcutaneous injections supports the replacement of enfuvirtide with newly available antiretrovirals, such as raltegravir, an integrase inhibitor administered orally. The EASIER-ANRS 138 clinical trial demonstrated that a switch to raltegravir was safe, well tolerated, and virologically noninferior to the maintenance of enfuvirtide in patients infected with multidrug-resistant HIV-1 infection who were receiving suppressive antiretroviral therapy. Although enfuvirtide is a peptide with no in vitro effect on drug-metabolizing enzymes or transporters, increases in saquinavir, lopinavir, and tipranavir concentrations when these protease inhibitors (PIs) were combined with enfuvirtide have been reported. Raltegravir is biotransformed mainly via glucuronidation and has been reported to not alter the pharmacokinetics of coadministered antiretrovirals. A pharmacokinetic substudy was designed in the ANRS 138 trial in order to assess a potential decrease in exposure of two protease inhibitors, tipranavir and darunavir, following the switch from enfuvirtide to raltegravir.

EASIER-ANRS 138 was an open-label, multicenter, randomized clinical trial that demonstrated noninferior antiviral efficacy at 24 weeks of a switch from enfuvirtide to raltegravir among treatment-experienced patients with suppression of plasma HIV-1 RNA below 400 copies/ml under the enfuvirtide-based regimen. The twenty patients enrolled in this trial gave their written informed consent to participate in the pharmacokinetic study. Nine patients were receiving ritonavir-boosted tipranavir (500/200 mg twice a day [BID]), and 11 patients were receiving ritonavir-boosted darunavir (600/100 mg BID) as part of their optimized background regimens.

Blood samples were drawn prior to the morning drug intake with a light continental breakfast and at 1 h, 3 h, 5 h, and 9 h postdosing when darunavir or tipranavir was combined with enfuvirtide (period 1), as well as at 24 weeks after the switch from enfuvirtide to raltegravir (period 2).

Tipranavir, darunavir, and ritonavir were assayed by validated high-performance liquid chromatography methods with UV detection, according to a previously described method that was modified. The lower limits of quantification of tipranavir, darunavir, and ritonavir were 400, 40, and 25 ng/ml, respectively. The coefficient of variation of quality control samples included in each analytical run was below 8%.

Pharmacokinetic parameters were calculated by a noncompartmental method (WinNonlin; Pharsight Corporation, Mountain View, CA). The area under the plasma concentration-time curve from 0 h to the last sampling time (9 h postdosing) (AUC₀⁻⁹) was determined at steady state and calculated according to the linear up/log down trapezoidal rule (WinNonlin; Pharsight, CA). The maximum concentration of drug observed in plasma (Cₘₓ), the observed predose concentration (C₀), and the time to Cₘₓ (Tₘₐₓ) were obtained from the plasma concentration-time curves. For each drug, 90% confidence intervals (90% CIs) for the geometric mean ratios (GMRs) (with enfuvirtide/with raltegravir) of C₀, Cₘₓ and AUC₀⁻⁹ were constructed and analyzed using a

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bioequivalence approach after log transformation (Statgraphics version 5.1; Manugistics, Inc., Rockville, MD).

Twenty patients were included in this pharmacokinetic study. Baseline characteristics of the 9 patients (8 males) on tipranavir and the 11 patients (9 males) on darunavir were the following: median ages, 47 and 49 years; median CD4 levels, 475 and 252 cells/\mu l; median durations of antiretroviral therapy, 13 years; percentages of viral loads below 50 copies/ml, 89% and 91%; and median weights, 60 and 79 kg, respectively. All but one patient also received nucleos(t)ide analog reverse transcriptase inhibitors [N(t)RTIs] in combination with PIs. A single patient in each PI group was on proton pump inhibitors.

The pharmacokinetic parameters calculated for darunavir, tipranavir, and ritonavir at period 1 with enfuvirtide (day 0) and period 2 after 24 weeks of raltegravir are compared in Table 1. Both tipranavir and darunavir concentrations decreased when enfuvirtide was switched to raltegravir (Fig. 1). The 90% CI of the GMR was lower than the bioequivalence range (0.80 to 1.25) for most parameters. Ritonavir concentrations were also higher when combined with enfuvirtide, although the decrease observed after the switch to raltegravir was modest, with a wide range of the 90% CI.

Daranavir and tipranavir exposure and interindividual variability were in agreement with previous pharmacokinetic data obtained from HIV-infected patients (1, 2, 12, 14). After switching from enfuvirtide to raltegravir, the concentrations of both of the protease inhibitors were significantly reduced. Such drug-drug interaction, although unexpected, has been observed previously for tipranavir-ritonavir, lopinavir-ritonavir, and saquinavir-ritonavir (6, 11). In the RESIST study, it has been reported that patients who were on enfuvirtide-based regimens had higher tipranavir concentrations than those who were not (11). Reasons for the observed decrease are presently unknown. An inhibitory effect of enfuvirtide or an inductive effect of raltegravir on cytochrome P450 3A (CYP3A) is unlikely, since on one hand, protease inhibitors were coadministered with ritonavir, a very potent CYP3A inhibitor, and on the other hand, no inductive effect for raltegravir has ever been reported (7). The effect of enfuvirtide or raltegravir on transporters cannot be ruled out, as there is increasing evidence that protease inhibitors are substrates of ABC or solute carrier (SLC) transporters (9, 10, 13). Garvey and collaborators reported that addition of raltegravir to a darunavir-ritonavir-tenofovir-emtricitabine regimen did not affect the darunavir concentration (5), which suggests that enfuvirtide increases protease inhibitor concentrations. Further studies should be conducted to assess whether enfuvirtide or raltegravir can affect the activity of such transporters, especially those expressed in enterocytes or hepatocytes. Unfortunately, low and variable rates of absorption do not allow comparison of terminal half-lives during a 12-h dosing interval, and therefore, there is no evidence showing whether the bioavailability, clearance, or possibly volume of distribution of protease inhibitors is impaired by enfuvirtide and/or raltegravir. Food effect is unlikely since protease inhibitors were taken with a light meal as a continental breakfast the day of the sampling for the pharmacokinetic study.

Despite this decrease in PI concentrations following the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tipranavir</th>
<th>Ritonavir-tipranavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Median concn (range) for indicated parameter</td>
<td>Period 1, week 0</td>
</tr>
<tr>
<td>C₀ (ng/ml)</td>
<td>42,201 (17,417–109,792)</td>
<td>15,321 (10,740–49,991)</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>71,329 (35,837–138,808)</td>
<td>50,501 (30,516–102,642)</td>
</tr>
<tr>
<td>T_max (h)</td>
<td>3.0 (1.0–5.0)</td>
<td>3.0 (2.5–5.0)</td>
</tr>
<tr>
<td>AUC₀–T (ng h/ml)</td>
<td>437,014 (212,973–1,165,190)</td>
<td>330,315 (171,030–786,218)</td>
</tr>
</tbody>
</table>

* Parameters were compared by GMRs and 90% CIs (shown in brackets).

FIG. 1. Mean plasma concentrations (and standard deviations) of tipranavir (n = 9) (A) or darunavir (n = 11) (B) when combined with enfuvirtide (open diamonds and solid lines) or raltegravir (closed squares and dotted lines).
switch from enfuvirtide to raltegravir, no virological failure in these patients for up to 48 weeks after the switch was observed, but the study was not powered to really assess the long-term virologic outcomes of this drug interaction (4).

In conclusion, this pharmacokinetic study has shown a small but significant decrease in tipranavir and darunavir concentrations following a switch from enfuvirtide to raltegravir. Further studies are needed to explain such an interaction and to assess the long-term virologic consequences of this observation.

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