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Decreased darunavir concentrations during once-daily co-administration with maraviroc and raltegravir: OPTIPRIM-ANRS 147 trial

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Background: The OPTIPRIM-ANRS 147 trial compared intensive combination ART (darunavir/ritonavir, tenofovir disoproxil fumarate/emtricitabine, raltegravir and maraviroc) started early during primary HIV-1 infection with standard tritherapy with darunavir/ritonavir, tenofovir disoproxil fumarate and emtricitabine. From month 6 to 18, the percentage of viral load values <50 copies/mL was lower in the pentatherapy arm than in the tritherapy arm. Here we compared antiretroviral drug concentrations between the two arms.

Methods: Plasma samples were collected from 50 patients at various times after drug administration. A Bayesian approach based on published population pharmacokinetic models was used to estimate residual drug concentrations (C_{trough}) and exposures (AUC) in each patient. A mixed linear regression model was then used to compare the AUC and C_{trough} values of each drug used in both groups.

Results: Published models adequately described our data and could be used to predict C_{trough} and AUC. No significant difference in tenofovir disoproxil fumarate, emtricitabine and ritonavir parameters was found between the two arms. However, darunavir C_{trough} and AUC were significantly lower in the pentatherapy arm than in the tritherapy arm ($P = 0.03$ and $P = 0.04$, respectively).

Conclusions: Adding maraviroc and raltegravir to darunavir-based tritherapy decreased darunavir concentrations. Compliance issues, maraviroc–darunavir interaction and raltegravir–darunavir interaction were suspected and may affect the kinetics of viral decay during pentatherapy. A specific pharmacokinetic interaction study is needed to explore the interactions between darunavir and maraviroc and raltegravir.

Introduction

The OPTIPRIM-ANRS 147 trial was designed to establish whether intensive combination ART (darunavir, ritonavir, tenofovir disoproxil fumarate/emtricitabine, raltegravir and maraviroc) started early during primary HIV-1 infection had a greater effect on the HIV reservoir than the recommended triple-drug regimen (darunavir/ritonavir, tenofovir disoproxil fumarate and emtricitabine).

This trial showed no additional benefit of pentatherapy on HIV-DNA levels.[1] On the contrary, although 60% of patients in the pentatherapy arm and only 31% of patients in the tritherapy arm had a viral load <50 copies/mL at 3 months ($P = 0.01$), the situation was reversed at 6 months (71% versus 89%), 12 months (78% versus 96%) and 18 months (82% versus 96%) ($P < 0.05$). This paradoxical result may have been due to lower antiretroviral exposure in the pentatherapy arm, because of pharmacological interactions or adherence issues.

The aim of the present study was thus to compare darunavir, ritonavir, emtricitabine and tenofovir concentrations and exposures between the tritherapy and pentatherapy arms of the OPTIPRIM-ANRS 147 trial.

Methods

Patients

OPTIPRIM-ANRS 147 was a randomized, open-label, Phase 3 trial involving 90 patients in 33 French hospitals. Complete details of the study protocol have been published elsewhere.[1] The study was approved by the Sud-Méditerranée-1 Ethics Committee and the French Health Products Safety Agency, and complied with the Helsinki Declaration. All participants gave written informed consent.

Treatment

Patients allocated to the standard regimen took four pills per day, consisting of 300 mg of tenofovir disoproxil fumarate plus 200 mg of emtricitabine (once daily), 800 mg of darunavir (two pills once daily), and 100 mg of ritonavir (once daily). Patients allocated to the intensive regimen took four additional pills: 400 mg of raltegravir (twice daily) and 150 mg of maraviroc (twice daily).

Sampling

Blood was sampled for pharmacokinetic analyses at 3, 6 and 24 months, at various intervals after drug administration. Age, body weight, serum creatinine and CD4+ cell counts were recorded.

Analytical methods

Plasma concentrations of darunavir, ritonavir, emtricitabine, tenofovir, raltegravir and maraviroc were determined at the Clinical Pharmacology Laboratory of Cochin Hospital, Paris, using validated LC-tandem MS methods. The lower limit of quantification was 10 ng/mL for emtricitabine, maraviroc, raltegravir, ritonavir and tenofovir, and 40 ng/mL for darunavir.

Pharmacokinetic analyses

Owing to sparse sampling and variable delays between sampling and drug intake, concentrations could not be compared directly between groups. A Bayesian approach, using models from the literature, was thus used to estimate the residual concentration and exposure for each drug in each patient. The choice was made after comparison of all population pharmacokinetic models available in the literature, in terms of the study population and the robustness of the model. To check that the chosen model was applicable to our data, OPTIPRIM-measured concentrations were superimposed on a visual predictive check (VPC) of the literature models. When there was no VPC in published models, we compared our data with published targets.

From the selected applied model, individual predicted parameters were determined for each patient in the OPTIPRIM dataset for the available sampling times, given the dosage history and the body weight, age and serum creatinine covariate values. The trough concentration (C_{trough}) and area under the curve from 0 to 12 or 24 h after last drug intake (AUC_{0-12} or AUC_{0-24}) were derived for each patient.

For each drug used in both arms, exposures and C_{trough} were compared between tritherapy and pentatherapy by means of a mixed linear regression model (random effect/patient). The darunavir C_{trough} was compared with a concentration of 550 ng/mL (10 times the IC_{50}). This model was applied to all the data (3, 6 and 24 months) and then, assuming that adherence would worsen over time, we constructed the same model with 3 month data only.

Results

Population characteristics

Only data with known times between sampling and drug intake were used for pharmacokinetic analysis. For this reason, data from 50 patients (92 concentrations) were used for the pharmacokinetic analysis, 22 in the tritherapy group and 28 in the pentatherapy group. At the time of the pharmacokinetic evaluation, the median age was 35.5 years (from 20 to 62 years) and the median body weight was 73.5 kg (from 42 to 119 kg) and comparable between groups. The median time after intake was 14.9 h (20 min to 29.7 h).

Bayesian approach

One population pharmacokinetic model was selected for each molecule: Moltó *et al.*[2] for darunavir, Baheti *et al.*[3] for tenofovir, Valade *et al.*[4] for emtricitabine, Chan *et al.*[5] for maraviroc and Arab-Alameddine *et al.*[6] for raltegravir. The concentrations measured in the OPTIPRIM trial were well described by VPC models in the literature (Figure 1), indicating these models were applicable to our data. Thus, a maximum *a posteriori* probability (Bayesian estimation) could be derived from these models to predict individual pharmacokinetic parameters for the six drugs. Exposures and C_{trough} of darunavir, ritonavir, emtricitabine, tenofovir, raltegravir and maraviroc are shown in Table 1. No significant differences between the two arms were found with respect to the AUC and C_{trough} of tenofovir, emtricitabine and ritonavir. The only significant differences concerned the AUC and C_{trough} of darunavir ($P = 0.03$ and $P = 0.04$, respectively). Only one patient in the tritherapy group (4.5%) and two patients in the pentatherapy group (7.1%) had a C_{trough} <550 ng/mL. To identify low adherence issues, exposures and C_{trough} were compared between 3, 6 and 24 months, but no significant difference was found.

Discussion

In the OPTIPRIM trial, virological efficacy was, surprisingly, lower in the pentatherapy arm than in the tritherapy arm at 6, 12 and 18 months ($P < 0.05$). One possible additional explanation was lower antiretroviral concentrations in the pentatherapy group, due to poorer adherence or to pharmacological interactions.

Regarding treatment adherence issues, the number of pills in the pentatherapy arm was greater (8 pills twice daily) than in the tritherapy arms (4 pills once daily). Concentrations measured in both groups corresponded to those reported in the literature, with no very low concentrations, and drug levels were not significant between 3, 6 and 24 months, arguing against an adherence problem. The proportion of patients in the PP population who stated that they had not missed a dose on the previous weekend was at least 90% at all visits except in the intensive combination ART group at month 18 ($P = 0.02$) and month 24 ($P = 0.18$) (data not shown).[1] However, concentrations were only determined in half the patients, and the measured concentrations only reflect adherence at the time of sampling.

There were no significant differences for AUC or C_{trough} of tenofovir, emtricitabine or ritonavir between the tritherapy and pentatherapy arms. However, the AUC and C_{trough} of darunavir differed significantly ($P = 0.03$ and $P = 0.04$, respectively). Few patients had a C_{trough} <550 ng/mL. This target concentration, which is used by

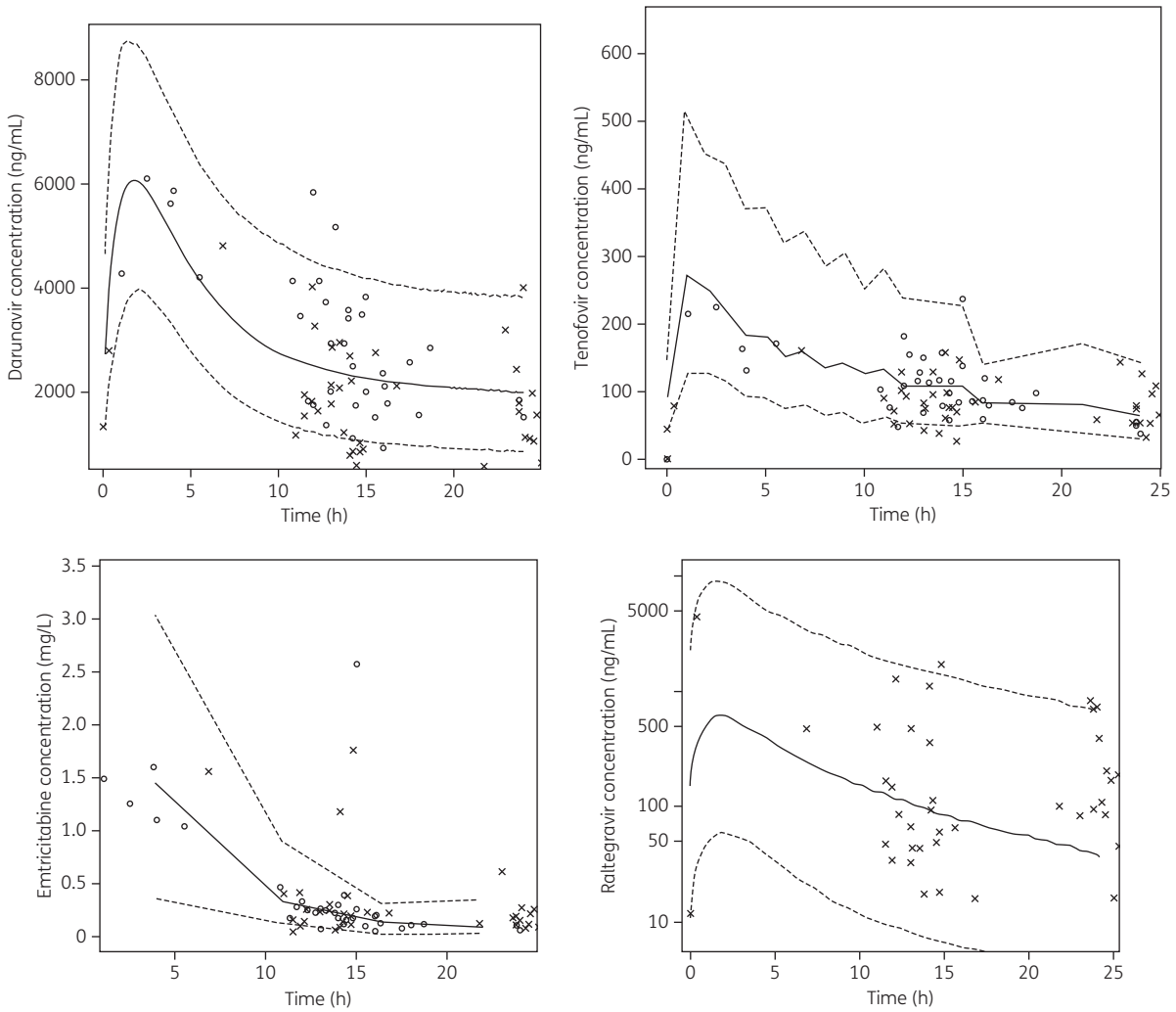

Figure 1. Visual inspection check (VPC) of darunavir, tenofovir, emtricitabine and raltegravir (as examples). Crosses, pentatherapy arm; circles, tritherapy arm.

Table 1. Bayesian estimates (AUC and C_{trough}) of darunavir, ritonavir, emtricitabine, tenofovir, raltegravir and maraviroc

	Total population	Tritherapy group	Pentatherapy group	*P*
AUC (ng·mL^{-1}·h), median (min–max)				
darunavir	63651 (28264–157030)	74481 (37882–157030)	57635 (28264–139400)	0.03*
ritonavir	6099 (417–46815)	5873 (417–46815)	6376 (726–43599)	0.72
emtricitabine	17000 (7599–73140)	16006 (7599–73140)	17880 (8669–53604)	0.55
tenofovir	4008 (1435–8739)	4026 (1435–8739)	3923 (1976–7060)	0.81
raltegravir	4123 (1216–58865)	–	4123 (1216–58865)	–
maraviroc	1736 (768–7532)	–	1736 (768–7532)	–
C_{trough} (ng/mL), median (min–max)				
darunavir	1599 (274–5182)	1989 (274–5182)	1388 (466–4496)	0.04*
ritonavir	39 (2–1220)	37.8 (2–1220)	42 (3–1093)	0.83
emtricitabine	154 (26–1995)	135 (26–1995)	171 (35–1262)	0.76
tenofovir	50 (5–223)	50 (7–223)	50 (5–147)	0.82
raltegravir	93 (11–4439)	–	93 (11–4439)	–
maraviroc	91 (20–472)	–	91 (20–472)	–

Asterisks indicate statistical significance ($P < 0.05$).

default, corresponds to 10 times the IC_{50} and is not a real pharmacokinetic–pharmacodynamic relationship. This substudy was too small to highlight a possible pharmacodynamic relationship between viral load and AUC or C_{trough}.

Compared with the tritherapy arm, the pentatherapy group received in addition raltegravir and maraviroc. Both drugs may be responsible for an interaction with darunavir.

Some findings supported the existence of raltegravir–darunavir interactions. Cattaneo *et al.*[7] showed that co-administration of raltegravir was associated with a 40% reduction in darunavir C_{max} and estimated AUC, but had no effect on C_{trough}. Taiwo *et al.*[8] provided clinical evidence that combined raltegravir/darunavir-based antiretroviral regimens may be less effective than other regimens. As raltegravir is two-thirds metabolized by UDP-glucuronosyltransferase, whereas darunavir is metabolized by cytochrome P450, this interaction was believed to be driven by induction of a drug transporter. Goldwirt *et al.*[9] found a small but significant decrease in darunavir concentrations in 10 patients following a switch from enfuvirtide to raltegravir. Fabbiani *et al.*[10] also reported a potential interaction between darunavir and raltegravir. Finally, in formal drug–drug interaction studies in healthy volunteers, raltegravir was also shown to decrease the pharmacokinetics of atazanavir (decreasing AUC and C_{trough} by 17% and 29%)[11] or amprenavir (decreasing AUC and C_{trough} by 19% and 33%).[12]

Other arguments support the existence of maraviroc–darunavir interactions. Firstly, both of them are mostly metabolized by CYP450 enzymes in the liver, and particularly by CYP3A4. The interaction is known to lead to a decrease in maraviroc dosage by 4-fold when coadministered with boosted PI. Kakuda *et al.*[13] studied interactions between darunavir/ritonavir, maraviroc and etravirine in healthy volunteers and showed that darunavir exposure and C_{trough} decreased by 15% and 25%, respectively, in the presence of maraviroc co-administration. In the OPTIPRIM study, the effect of maraviroc on darunavir C_{trough} could have been more pronounced because of a once-daily rather than twice-daily administration. In other studies without pharmacokinetic data, the virological efficacy of maraviroc plus darunavir/ritonavir was inferior to darunavir/ritonavir plus tenofovir/emtricitabine.[14]

Finally, the slight difference in the darunavir AUCs in the pentatherapy group could contribute to explaining the different virological results in the OPTIPRIM study as due to less efficient diffusion in the HIV reservoir caused by a lower plasma concentration, limiting tissue diffusion and hence reducing the impact on residual viral replication in the pentatherapy arm.[15,16] A different hypothesis could explain this difference: lower compliance in the pentatherapy group; interaction between darunavir and raltegravir; or interaction between darunavir and maraviroc. A combined regimen with these drugs could be an option in particular situations at the chronic stage. Therefore it would be relevant to evaluate, in a specific pharmacokinetic interaction study, the interactions between darunavir, maraviroc and raltegravir.

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