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A. Calcagno1,*, M. C. Tettoni1, M. Simiele2, L. Trentini1, C. Montrucchio1, A. D'Avolio2, G. Di Perri1 and S. Bonora1

1Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

2Laboratory of Clinical Pharmacology and Pharmacogenetics, Department of Medical Sciences, University of Torino, Torino, Italy

*Corresponding author. Tel: +390114393884; Fax: +390114393818;

E-mail: andrea.calcagno@unito.it

Sir,

Long-term side effects and medication costs are driving research on antiretroviral therapy towards dose-optimization and dose-reduction strategies. Two main factors are supporting this trend: the knowledge that doses lower than those adopted for clinical use are equally effective (as seen in Phase II studies of most antiretrovirals),1 and the increasing evidence of immunovirological efficacy of simplified regimens consisting of fewer than three drugs, particularly in induction–maintenance strategies. One of the major interests in this setting is to validate regimens devoid of nucleoside/nucleotide reverse transcriptase inhibitors (N/NtRTIs), and several small-sized clinical studies are investigating the efficacy of different N/NtRTI-sparing combinations. The raltegravir and atazanavir dual combination was found to be effective in a comparative study in treatment-naive patients, but the trial was prematurely stopped following the excess of resistance to raltegravir in those who experienced virological failure.2 In this study, however, a non-conventional twice-daily unboosted atazanavir dosage was employed (300 mg), possibly resulting in raltegravir monotherapy in case of suboptimal adherence. Based on the results of the dose-finding Phase II study of raltegravir (in which twice-daily doses ranging from 100 to 600 mg were found to be immunovirologically equivalent at 48 weeks),3 on two small reports of once-daily dosing of 400 mg of raltegravir4,5 and on the property of atazanavir to increase raltegravir exposure (by UGT1A1 inhibition),6 we carried out a pilot clinical investigation to evaluate the raltegravir pharmacokinetic profile when administered at 400 mg once daily with boosted atazanavir-based regimens.

Adult HIV-infected patients without severe clinical comorbidities and on successful treatment with atazanavir/ritonavir plus two N/NtRTIs had their regimens intensified for 10 days with 400 mg of raltegravir once daily. The protocol was approved by our local ethics board and each participant gave written informed consent. Serial plasma samples for pharmacokinetic analysis were collected

on day 10 at pre-dose (0 h) and 1.5, 3, 4.5, 6, 8, 12 and 24 h after the morning dose. Plasma concentrations were measured by a validated HPLC-PDA (where PDA is photo diode array) method [limit of detection (LOD) 11 ng/mL].7 Steady-state pharmacokinetic parameters were derived by non-compartmental analysis using the validated computer program Kinetica and are expressed as medians and interquartile ranges.

The eight patients enrolled were mainly male (7, 87.5%) and middle-aged [48.5 years (48–62)] and their body mass index was 21.8 kg/m2 (19.3–24.4). HIV RNA was <20 copies/mL in all patients and the CD4 count was 190 cells/μL (86–288); two patients (25%) presented a chronic infection with HCV. Concomitant N/NtRTIs included tenofovir/emtricitabine (five patients) and abacavir/lamivudine (three patients). Plasma creatinine and estimated glomerular filtration rate were 1.01 mg/dL (0.97–1.32) and 69.3 mL/min/24 h (67.7–72.8), respectively. Raltegravir AUC, Cmax, C24, half-life and clearance were, respectively, 17 547 ng · h/mL (14 212–33 132), 4200 ng/mL (3885–6655), 51 ng/mL (28–58), 3.4 h (2.8–4.5) and 23.2 L/h (12.1–28.1) (Figure 1). Raltegravir pre-dose and C24 were below the LOD in one patient. Atazanavir AUC, Cmax, C24, half-life and clearance were, respectively, 26 414 ng · h/mL (23 679–46 799), 2625 ng/mL (1920–3904), 526 ng/mL (355–908), 10.6 h (9.0–13.0) and 11.3 L/h (7.3–12.7). Ritonavir AUC, Cmax, C24, half-life and clearance were, respectively, 11 873 ng · h/mL (8373–20 727), 1205 ng/mL (1053–1910), 99 ng/mL (54–166), 5.6 h (4.8–6.3) and 8.7 L/h (4.8–11.9).

With the limitation of a single-arm protocol, this pilot study shows that half-dose raltegravir exposure, when combined with atazanavir/ritonavir, seems to be adequate in the majority of patients, with just one trough concentration (out of 16 measurements considering both C0 and C24) reported to be below the 95% inhibitory concentration for the wild-type virus. Although Cmax appeared to be slightly higher and C24 slightly lower than the historical data with the twice-daily dosing (2170 versus 4200 ng/mL and 68.6 versus 51 ng/mL, respectively), plasma exposure of

400 mg of raltegravir once daily in our study was equivalent to 800 mg once-daily dosing without atazanavir or standard 400 mg twice-daily dosing. Specifically, the raltegravir AUC0–24 of our patients was similar to the AUC0-24 of the 800 mg once-daily dosage in the QDMARK study (14 895 ng·h/mL) and 2-fold higher than the reported AUC0–12 values with standard 400 mg twice-daily dosage (6340–6910 ng · h/mL).8,9 It must be noted that in the QDMRK study the difference in the virological response between the two arms (raltegravir once daily versus twice daily) was seen only in those who started with a baseline viraemia >100 000 copies/mL, in association with a Ctrough <33 nM (15 ng/mL).2 Neely et al.10 previously described lower raltegravir exposure when associated with atazanavir as compared with our results, but different dosing (unboosted versus boosted atazanavir) and study design (healthy volunteers versus patients) could explain these differences. Atazanavir concentrations were comparable to historical data and Ctrough values were above the target level (150 ng/mL) in all patients. On a presumptive basis, the pharmacokinetic exposure of the raltegravir dose of 400 mg once daily seen in our patients in association with atazanavir/ritonavir might be sufficient to provide adequate antiretroviral coverage in an induction–maintenance strategy; should this drug combination prove to be successful in a clinical study, it would enable a reduction in both N/NtRTI-related toxicity and drug expenditure.

Funding

This work was funded by internal funding.

Transparency declarations

A. C. has received travel grants or speaker's honoraria from Abbott, Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD) and Janssen-Cilag. G. D. P. has received grants, travel grants and consultancy fees from Abbott, Boehringer Ingelheim, BMS, Gilead Sciences, GSK, MSD, Pfizer, Roche and Tibotec (Johnson & Johnson). S. B. has received grants, travel grants and consultancy fees from Abbott, Boehringer Ingelheim, BMS, Gilead Sciences, GSK, MSD, Pfizer and Janssen-Cilag. All other authors: none to declare.

Acknowledgements

The data in this manuscript were presented at the Thirteenth International Workshop on Clinical Pharmacology of HIV Treatment (IWCPHT), Barcelona, Spain, 2012 (Poster P_05).

We would like to thank the study participants and to acknowledge the great help by the nurses that allowed sample collection and processing.

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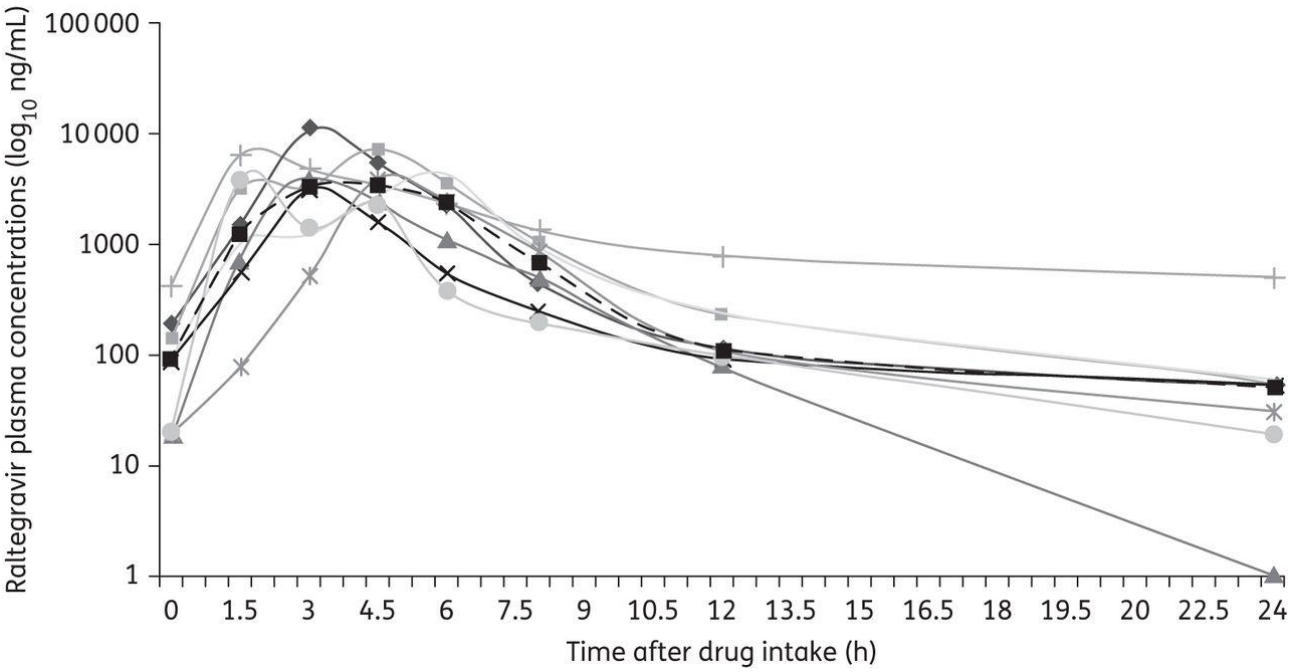

Figure 1.

Raltegravir log10-transformed concentrations (log10 ng/mL) according to time post-dose (h) when administered as 400 mg once daily in association with atazanavir/ritonavir/two N/NtRTIs. Every continuous line represents a single patient profile while the broken line is the median of the studied population.