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SHORT COMMUNICATION

Pharmacokinetics of the combination raltegravir/atazanavir in HIV-1-infected patients*

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Objectives

To evaluate the use of raltegravir with unboosted atazanavir in combination with one nucleoside reverse transcriptase inhibitor (NRTI) (lamivudine or emtricitabine) as a potentially well-tolerated once-daily (qd) maintenance regimen.

Methods

We compared the pharmacokinetics of raltegravir 400 mg twice daily (bid) with raltegravir 800 mg qd in HIV-infected patients ($n = 17$) on unboosted atazanavir (600 mg qd) in combination with lamivudine or emtricitabine.

Results

The area under the plasma concentration *vs*. time curve for a dose interval t (AUC_{0-t}) of 800 mg qd divided by 2 was not significantly different from the AUC_{0-t} of 400 mg bid ($P = 0.664$) but the minimum concentration (C_{min}) was 72% lower with the qd regimen ($P = 0.002$). The regimen was well tolerated and the viral load remained undetectable in all patients during the 6 weeks of the study follow-up.

Conclusions

A qd regimen of raltegravir 800 mg, atazanavir 600 mg and lamivudine or emtricitabine resulted in favourable pharmacokinetic profiles and good short-term safety and efficacy data. Larger phase IIb studies are needed to explore this novel regimen.

Keywords: antiretroviral agents, atazanavir, drug interactions, HIV integrase inhibitor, pharmacokinetics, raltegravir

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Introduction

Antiretroviral treatment guidelines currently recommend regimens containing two nucleoside reverse transcriptase inhibitors (NRTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a ritonavir-boosted protease inhibitor (PI) or an integrase inhibitor [1]. Significant toxicity has been associated with ritonavir-boosted PI-containing regimens. Indeed, even at low doses, administration of ritonavir is associated with dyslipidaemia. In addition, ritonavir causes complex pharmacokinetic drug interactions and causes gastrointestinal (GI) adverse effects. Because of these disadvantages, it would be useful to have an antiretroviral regimen that does not contain ritonavir. Atazanavir (unboosted) is a PI that has a less undesirable effect on the lipid profile and has good GI tolerability [2]. Unboosted atazanavir with two NRTIs, however, is not a preferred first-line regimen [1].

Current evidence also supports use of the combination of two NRTIs and raltegravir [1]. Raltegravir does not seem to have negative effects on lipid levels and it is generally safe

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and well tolerated [3]. The recommended dose of raltegravir is 400 mg twice daily (bid). It is metabolized predominantly through glucuronidation by UDP-glucuronosyltransferase 1A1 (UGT1A1). Atazanavir is a UGT1A1 inhibitor. Previous pharmacokinetic studies in healthy volunteers have shown that atazanavir 400 mg once daily (qd) increases plasma concentrations of raltegravir 400 mg bid by 72% [4]. This suggests that combined use of atazanavir and qd raltegravir is possible.

Raltegravir with unboosted atazanavir in combination with one well-tolerated NRTI (lamivudine or emtricitabine) would be expected to be a well-tolerated qd maintenance regimen.

Methods

We designed this open-label, sequential, two-period, multicentre, phase II, multiple-dose maintenance study to compare the pharmacokinetics of raltegravir 400 mg bid *vs.* 800 mg qd by intrasubject comparison. Secondary objectives were to evaluate the safety and efficacy of this regimen. HIV-1-infected patients who were at least 18 years old were eligible if their HIV-1 RNA had been < 40 HIV-1 RNA copies/mL for at least the previous 6 months; patients with documented resistance mutations were excluded. Other exclusion criteria were active hepatic disease (including chronic hepatitis B virus infection), pregnancy, abnormal serum transaminases, and concomitant use of medications that interfered with raltegravir or atazanavir pharmacokinetics.

The study was approved by the Medical Ethical Committees of the participating centres. All patients gave written informed consent to participate. The study was performed in two periods of 4 weeks each. In the first period, patients received raltegravir 400 mg bid, atazanavir 600 mg qd and lamivudine 300 mg qd or emtricitabine 200 mg qd. In this study, a dose increase of atazanavir to 600 mg was applied to compensate for the mild reduction in atazanavir plasma concentrations [5]. At week 2, a 24-hour pharmacokinetic curve, the viral load and the trough concentration (C_{trough}) of atazanavir were determined. If at week 2 the viral load was still undetectable (< 40 copies/mL), the C_{trough} for atazanavir was > 0.12 mg/L and the regimen was well tolerated, patients entered the second period of the study. In this period, subjects received raltegravir 800 mg qd; the doses of the other antiretroviral drugs remained unchanged. At week 6, another 24-hour pharmacokinetic curve, the viral load and the C_{trough} of atazanavir were determined.

Plasma concentrations of raltegravir and atazanavir were determined using validated high-performance liquid chromatography (HPLC) assays for raltegravir [limit of quantification (LOQ) 0.014 mg/L] and atazanavir (LOQ 0.045 mg/L). Pharmacokinetic parameters were calculated with noncompartmental methods using the WinNonlin software package (version 5.2; Pharsight, Mountain View, CA). Paired *t*-tests were carried out to compare raltegravir 400 mg bid with 800 mg qd using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL).

Results

A total of 19 patients (three of whom were female) were enrolled in the study; the median (range) age was 44 [37–75] years, and the median (range) BMI was 24 [20–36] kg/m^2. One patient discontinued the study because of an adverse reaction, and one patient had an atazanavir dose increase because of a low C_{trough}. Seventeen patients were therefore included in the statistical evaluation. The regimens used before the start of the study were NNRTI-based regimens (three patients), boosted PI-based regimens (14 patients, of whom nine used ritonavir-boosted atazanavir) and raltegravir-based regimens (two patients).

Table 1 and Figure 1 show the pharmacokinetic parameters of raltegravir. The geometric mean area under the plasma concentration *vs.* time curve for a dose interval *t* (AUC_{0-t}) of raltegravir 800 mg qd was 82% [90% confidence interval (CI) 26–163%] higher than the AUC_{0-t} of 400 mg bid. The AUC_{0-t} of 800 mg qd divided by 2 was not significantly different from the AUC_{0-t} of 400 mg bid ($P = 0.664$). The mean minimum concentration (C_{min}) for 800 mg qd raltegravir was 72% (90% CI 50–85%) lower ($P = 0.002$) than for 400 mg bid. Pharmacokinetic parameters of atazanavir were similar during the two raltegravir dosing regimens.

During the study no serious adverse events were reported. One patient dropped out in period 1 because of a grade III transaminase elevation [aspartate aminotransferase (AST)/alanine aminotransferase (ALT)]; the patient recovered from this adverse event. Four other patients reported adverse events but these were judged not to be related to study medication. In patients previously treated with atazanavir/ritonavir, median bilirubin levels decreased from 49 μM (2.9 mg/dL) to 24 μM (1.4 mg/dL); in patients naïve to atazanavir, bilirubin levels increased from 10 μM (0.58 mg/dL) to 13 μM (0.76 mg/dL) [normal value: < 21 μM (1.2 mg/dL)]. All patients had an undetectable viral load up to week 6 (end of study).

Discussion

This study showed that, in the presence of unboosted atazanavir 600 mg qd, raltegravir 800 mg qd resulted in an AUC that was similar to the AUC obtained with raltegravir 400 mg bid. The regimen was well tolerated and the viral

Table 1 Raltegravir pharmacokinetics (PK)

PK parameter†	Reference [7] RAL 400 mg bid LSM (CV%)	Period 1 RAL 400 mg bid GM (95% CI)	Period 2 RAL 800 mg qd GM (95% CI)	qd *vs.* bid GMR (90% CI)	*P*-value
Raltegravir					
$AUC_{0\rightarrow t}$ (h/mg/L)	6.34 [99]	7.5 (5.4–10.5)	13.7 (9.6–19.6)	1.82 (1.26–2.63)	0.012
$AUC_{0\rightarrow t}$ (h/mg/L)*		7.5 (5.4–10.5)	6.9 (4.8–9.8)*	0.91 (0.63–1.32)*	0.664
C_{max} (mg/L)	1.06 [135]	1.9 (1.4–2.6)	2.6 (1.8–3.7)	1.36 (0.93–2.00)	0.177
T_{max} (h)		2.1 (1.1–4.0)	2.7 (2.0–4.0)		
C_{min} (mg/L)	0.08 [167]	0.09 (0.05–0.16)	0.03 (0.01–0.05)	0.28 (0.15–0.50)	0.002
$T_{½}$ (h)		1.9 (1.5–2.6)	3.7 (2.9–4.9)	1.91 (1.47–2.49)	0.001
Atazanavir					
$AUC_{0\rightarrow t}$ (h/mg/L)		42.8 (34.1–53.8)	46.0 (39.3–53.9)	1.08 (0.92–1.25)	0.352
C_{max} (mg/L)		7.1 (6.0–8.3)	7.5 (6.7–8.4)	1.06 (0.92–1.23)	0.485
T_{max} (h)		3.0 (1.5–4.0)	3.0 (0.8–4.0)		0.394
C_{min} (mg/L)		0.36 (0.23–0.56)	0.31 (0.24–0.41)	0.86 (0.64–1.15)	0.605
$T_{½}$ (h)		5.9 (5.1–6.7)	5.4 (4.8–6.1)	0.93 (0.85–1.00)	0.156

$AUC_{0\rightarrow t}$, area under the plasma concentration *vs.* time curve for a dose interval t; bid, twice daily; C_{min}, minimum concentration; C_{max}, maximum concentration; CI, confidence interval; CV%, coefficient of variation; GM, geometric mean; GMR, geometric mean ratio; LSM, least-squares mean; RAL, raltegravir; qd, once daily; T_{max}, time of maximum plasma concentrate; $T_{1/2}$, elimination half-life.
*$AUC_{0\rightarrow t}$ for period 2 is divided by 2 to compare the qd regimen with the bid regimen.
†Values are given as geometric mean (95% confidence interval), except for T_{max} where median (interquartile range) are presented.

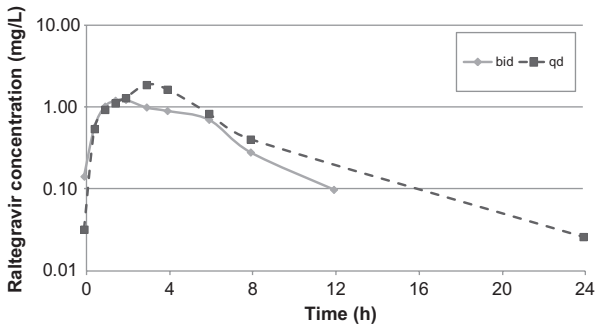

Fig. 1 Raltegravir plasma concentration *vs.* time curve for 400 mg twice daily (bid) and 800 mg once daily (qd).

load remained undetectable in all patients during 6 weeks of follow-up.

An analysis of phase III studies with raltegravir 400 mg bid could not find a relationship between raltegravir C_{min} and antiviral response [6]. Recently, data from the QDMRK study indicated that treatment-naïve patients on 800 mg qd raltegravir with two NRTIs with high baseline viral load had significantly lower antiviral response than patients on 400 mg bid raltegravir with two NRTIs [7]. A pharmacokinetic/pharmacodynamic analysis showed that the majority of failures could be explained by high baseline viral load and low raltegravir C_{min} values [6]. Although no formal cut-off for raltegravir C_{min} was given, patients with C_{min} values in the lowest quartile (0.003–0.021 mg/L) had a significantly lower antiviral response than patients in the other quartiles. In our study, six of 17 patients had C_{min} in this range while on 800 mg qd *vs.* three of 18 patients on 400 mg bid, but this was not associated with short-term loss of viral suppression. Notably, our study differs in three major respects from QDMRK: (1) in our study, maintenance therapy was assessed *vs.* initial therapy in QDMRK; (2) there was boosting of qd raltegravir with atazanavir in our study *vs.* no boosting in QDMRK; (3) there was qd dosing of raltegravir with a PI and one NRTI in our study *vs.* qd dosing of raltegravir plus two NRTIs in QDMRK.

Previous studies [8–10] on dual therapy with raltegravir and atazanavir (without NRTIs) showed that the regimen had a favourable lipid profile. One concern was the relatively high incidence of virological failures on this dual regimen, when patients initiated treatment with high baseline viral loads. Another issue was increased rates of hyperbilirubinaemia as a result of high atazanavir trough concentrations when it was dosed bid [7]. Our regimen contained atazanavir unboosted qd, leading to lower atazanavir trough concentrations without significant numbers of cases of hyperbilirubinaemia.

Patients were allowed to continue with the study regimen after study closure at the discretion of the treating physician and the patient. Post study data collected from medical records of the 12 patients who had chosen to continue with the study regimen showed that after 24 weeks 11 patients (92%) still had undetectable viral load; one nonadherent patient experienced virological failure (resistance data unknown). After 48 weeks, one additional patient had stopped because of viral blip (90 copies/mL); the remaining 10 patients (83%) maintained undetectable viral loads. The majority of these patients have now > 96 weeks of follow-up with no additional failures. This study, however, was not

designed or powered to determine the long-term safety and efficacy of this particular qd regimen.

In conclusion, a qd regimen of raltegravir 800 mg, atazanavir 600 mg and lamivudine or emtricitabine resulted in favourable pharmacokinetic profiles and good short-term safety and efficacy data. Larger phase IIb studies are needed to explore this novel regimen.

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Clinical trial registration: NCT00943540.

Conflicts of interest: DMB has received honoraria for serving on advisory boards, speaker's fees, and educational grants for clinical research from Merck, the manufacturer of raltegravir, and from Bristol-Myers Squibb, the manufacturer of atazanavir. JR has received honoraria for serving on advisory boards as well as speaker's fees from Abbott, Bionor, BMS, BI, Merck, GSK, Gilead, Pfizer, ViiV and Tibotec. J-CW has received speaker's fees and advisory honoraria from Bristol-Myers Squibb. All other authors declare no conflict of interest.

References

1 Thompson MA, Aberg JA, Hoy JF *et al.* Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA* 2012; **308**: 387–402.

2 Le Tiec C, Barrail A, Goujard C, Taburet AM. Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. *ClinPharmacokinet* 2005; **44**: 1035–1050.

3 Steigbigel RT, Cooper DA, Teppler H *et al.* Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 phase iii trials. *ClinInfectDis*. 2010; **50**: 605–612.

4 Iwamoto M, Wenning LA, Mistry GC *et al.* Atazanavir modestly increases plasma levels of raltegravir in healthy subjects. *ClinInfectDis*. 2008; **47**: 137–140.

5 Zhu L, Butterton J, Persson A *et al.* Pharmacokinetics and safety of twice-daily atazanavir 300 mg and raltegravir 400 mg in healthy individuals. *AntivirTher.* 2010; **15**: 1107–1114.

6 Rizk ML, Hang Y, Luo WL *et al.* Pharmacokinetics and pharmacodynamics of once-daily versus twice-daily raltegravir in treatment-naive HIV-infected patients. *Antimicrob Agents Chemother* 2012; **56**: 3101–3106.

7 Eron JJ, Jr, Rockstroh JK, Reynes J *et al.* Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial. *Lancet Infect Dis* 2011; **11**: 907–915.

8 Cordery DV, Hesse K, Amin J, Cooper DA. Raltegravir and unboosted atazanavir dual therapy in virologically suppressed antiretroviral treatment-experienced HIV patients. *Antiviral Therapy.* 2010; **15**: 1035–1038.

9 Cattaneo D, Ripamonti D, Baldelli S, Cozzi V, Conti F, Clementi E. Exposure-related effects of atazanavir on the pharmacokinetics of raltegravir in HIV-1-infected patients. *Ther Drug Monit* 2010; **32**: 782–786.

10 Kozal MJ, Lupo S, DeJesus E *et al.* A nucleoside- and ritonavir-sparing regimen containing atazanavir plus raltegravir in antiretroviral treatment-naive HIV-infected patients: SPARTAN study results. *HIV Clinical Trials*. 2012; **13**: 119–130.