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Atazanavir/ritonavir monotherapy: 96 week efficacy, safety and bone mineral density from the MODAt randomized trial

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Objectives: To report the 96 week results on efficacy, safety and bone mineral density (BMD) in subjects with HIV-1 that were virologically suppressed and treated with atazanavir/ritonavir monotherapy versus atazanavir/ritonavir triple therapy.

Methods: MODAt is a prospective, multicentre, open-label, non-inferiority, randomized, 96 week trial (NCT01511809) comparing efficacy of atazanavir/ritonavir monotherapy versus atazanavir/ritonavir triple therapy. Treatment success was defined as no occurrence of confirmed viral rebound (two consecutive HIV-RNA >50 copies/mL) or discontinuation for any cause of the ongoing regimen.

Results: The 96 week treatment success was 64% in the atazanavir/ritonavir monotherapy arm and 63% in the triple-therapy arm (difference 1.3%, 95% CI: −17.5 to 20.1). In the atazanavir/ritonavir monotherapy arm, no PI- or NRTI-associated resistance mutations were observed at virological failure and all patients re-suppressed after re-intensification. In the monotherapy arm, treatment failure was more frequent in patients coinfected with hepatitis C virus [64% versus 28% (difference 35.4%, 95% CI: 3.7–67.2)]. Drug-related adverse events leading to discontinuation were 3 (6%) in the atazanavir/ritonavir monotherapy arm and 11 (21.5%) in the triple-therapy arm ($P=0.041$). The 96 week adjusted mean percentage change in total proximal femur (not at lumbar spine) BMD was +1.16% and −1.64% in the atazanavir/ritonavir monotherapy arm and the triple-therapy arm, respectively ($P=0.012$).

Conclusions: The 96 week analyses suggested that long-term efficacy of atazanavir/ritonavir monotherapy was inferior as compared with atazanavir/ritonavir triple therapy, particularly when administered in subjects coinfected with hepatitis C virus. In the atazanavir/ritonavir monotherapy arm, reintroduction of nucleosides, as needed, was always effective with no new resistance mutation; monotherapy was also associated with a lower incidence of adverse events and improvement in femur BMD.

Introduction

Several clinical trials analysed the 96 week efficacy and safety of lopinavir/ritonavir[1–8] or darunavir/ritonavir[9–11] monotherapy in patients with HIV that were virologically suppressed and their results showed a lower efficacy of ritonavir-boosted PI (PI/r) monotherapy than triple therapy in maintaining virological suppression. The 48 week results of the **M**onotherapy **O**nce a **D**ay with **At**azanavir/r (MODAt) study[12] showed an inferior virological efficacy of atazanavir/ritonavir monotherapy in

comparison with triple therapy, which was promptly retrieved by the reintroduction of NRTIs.

The MODAt study assessed changes in bone mineral density (BMD), which was not investigated by any of the previously mentioned randomized trials.[1–11]

Here, the aim was to report the 96 week results of the MODAt study on efficacy, safety and BMD.

Patients and methods

The MODAt study is a prospective, multicentre, open-label, non-inferiority, randomized, 96 week trial (NCT01511809) in patients on atazanavir/ritonavir plus two NRTIs, fully suppressed and without previous virological failure, whose study design and methodology have been previously reported.[12] The protocol was approved by the Ethics Committee of each participating site and all the enrolled patients provided written informed consent.

Patients underwent a clinical assessment and routine laboratory tests at screening, baseline and at weeks 4, 8, 12, 16, every 8 weeks until week 48 and then every 12 weeks until week 96 or discontinuation.

At baseline, week 48, week 96 or at discontinuation, patients underwent standardized DEXA scan to evaluate BMD of the lumbar spine and total proximal femur; at baseline, the following bone biomarkers were tested: osteocalcin, 25-OH vitamin D, receptor activator of NF-κB ligand (RANKL), osteoprotegerin and cross-linked carboxy-terminal telopeptide of type I collagen (CTX-I).

Treatment success was defined as not having the following events: confirmed viral rebound (CVR; two consecutive HIV-RNA values >50 copies/mL) or treatment discontinuation for any cause. In case of CVR, patients treated with atazanavir/ritonavir monotherapy re-intensified with their previous two NRTIs and, if not suppressed (HIV-RNA <50 copies/mL) after 12 weeks, discontinued the study; patients treated with atazanavir/ritonavir triple therapy had to be discontinued from the study.

The primary endpoint was the proportion of patients with treatment success by week 48. Secondary endpoints included the proportion of patients with treatment success by week 96, changes in CD4+, changes in safety parameters and BMD.

Statistical analysis

The MODAt trial was designed to show non-inferiority in the 48 week efficacy of atazanavir/ritonavir monotherapy as compared with atazanavir/ritonavir triple therapy.[12] A pre-specified interim analysis on the first 100 patients with 48 weeks of follow-up was performed: an independent Data and Safety Monitoring Board, in June 2013, recommended to stop patients' enrolment based on the efficacy results and, according to the safety results, to continue to follow-up enrolled patients until 96 weeks, after signing an updated informed consent.

The primary 96 week efficacy analysis was performed on the ITT population considering patients treated with atazanavir/ritonavir who re-intensified due to CVR as failure (ITT with re-intensification=failure) as well as discontinuations for any reason or loss to follow-up. The 96 week efficacy analyses were also performed considering re-intensification equals success [ITT with re-intensification=success, if patient with CVR achieved virological suppression (HIV-RNA <50 copies/mL) within 12 weeks since reintroduction of NRTIs].

The analyses on the other secondary endpoints were performed on the ITT population, using the re-intensification=failure approach.

All data are summarized as median (IQR) or proportions.

The χ^2 test or Fisher's exact test and the Wilcoxon rank sum test were used to compare discrete and continuous variables, respectively. Significant 96 week changes from baseline were evaluated by the Wilcoxon signed rank test.

Linear regression was applied to evaluate the predictors [age, gender, BMI, smoking, hepatitis C virus (HCV), baseline CD4+, study arm, vitamin D or calcium supplementation, baseline osteocalcin, baseline RANKL, baseline vitamin D, baseline osteoprotegerin and baseline CTX-I] of 96 week percentage changes from baseline in vertebral and total proximal femur BMD; all factors known to influence BMD change and all the tested bone biomarkers were entered into the multivariate model.

The analyses were performed using SAS Software, release 9.2 (SAS Institute, Cary, NC, USA).

Results

A total of 103 patients were initially randomized;[12] 73 reached week 96 [41 in the atazanavir/ritonavir monotherapy (32 with no re-intensification) arm and 32 (63%) in the atazanavir/ritonavir triple-therapy arm (Figure S1, Table S1 and Table S2, available as Supplementary data at *JAC* Online)].

Efficacy

Results of the efficacy analyses according to the study arm are reported in Figure 1. In the ITT analysis with re-intensification=failure, efficacy was 64% (32 of 50) in the monotherapy arm and 63% (32 of 51) in the triple-therapy arm (difference 1.3%, 95% CI: −17.5 to 20.1). In the ITT with re-intensification=success, 82% (41 of 50) in the monotherapy arm and 63% (32 of 51) in the triple-therapy arm were in the study at week 96 (difference 19.3%, 95% CI: 2.2–36.3). Fourteen patients in the monotherapy arm had a median HIV-RNA of 136 (72–376) copies/mL; no PI- or NRTI-associated resistance mutations were observed at CVR and all patients re-suppressed after re-intensification. In the monotherapy arm, treatment failure was more frequent in patients coinfected with HCV [64% versus 28% (difference 35.4%, 95% CI: 3.7–67.2)].

A similar 96 week increase in CD4+ cell counts since baseline was observed in either arms (Figure 1).

Safety

Serious adverse events (AEs) occurred in four (8%) patients in the monotherapy arm and two (4%) in the triple-therapy arm ($P=0.436$).

Drug-related AEs leading to discontinuation were 3 (6%) in the monotherapy arm and 11 (21.5%) in the triple-therapy arm ($P=0.041$).

Grade 3–4 AEs were 9 (18%) in the monotherapy arm and 22 (43%) in the triple-therapy arm ($P=0.009$) (1 of 9 in the atazanavir/ritonavir arm and 9 of 22 in the atazanavir/ritonavir triple-therapy arm were drug related: $P=0.016$).

Changes of safety parameters reported at week 48 among patients treated with atazanavir/ritonavir monotherapy were also maintained over the 96 week follow-up (Figure S2): at 96 weeks, subjects on atazanavir/ritonavir monotherapy, and not on triple therapy, showed a significant increase in total cholesterol [19 (−1 to 31) mg/dL, $P=0.0001$], LDL-cholesterol [6 (−11 to 22) mg/dL] together with an amelioration of fasting glucose [−4 (−10 to 3) mg/dL, $P=0.040$], HDL-cholesterol [4 (−1 to 9) mg/dL, $P=0.0005$], estimated glomerular filtration rate [6.3 (−4.3 to 21.1) mL/min/1.73 m^2, $P=0.004$], phosphate [0.05 (−0.04 to 0.16) mg/dL, $P=0.022$] and alkaline phosphatase [−16 (−28 to −8) U/mL, $P<0.0001$]. No differences between study arms were observed with respect to changes from baseline in total bilirubin, transaminases, liver fibrosis markers, triglycerides and creatinine.

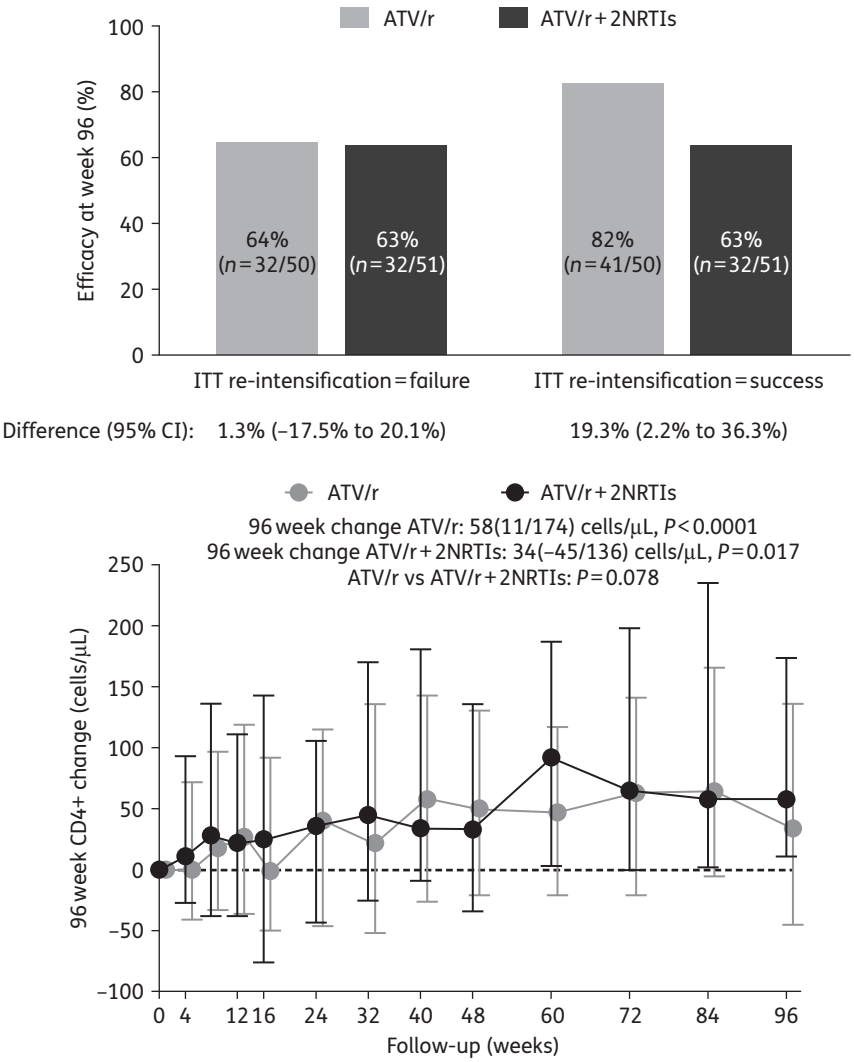

Figure 1. MODAt trial: 96 week treatment efficacy and median (IQR) changes from baseline in CD4+ cell count. ATV/r, atazanavir/ritonavir.

BMD and bone biomarkers

Sixty-nine subjects had available BMD data at baseline and week 96 or discontinuation (29 patients on atazanavir/ritonavir monotherapy with no re-intensification and 40 patients on atazanavir/ritonavir triple therapy).

The 96 week percentage change in BMD either at total proximal femur or at lumbar spine was more favourable in patients treated with atazanavir/ritonavir monotherapy than those on triple therapy (Table 1); in addition, subjects on atazanavir/ritonavir monotherapy with RANKL <32 pg/mL (median value) were associated with the highest femoral BMD increase at week 96.

Discussion

The 96 week efficacy analysis of the MODAt study suggested that virological efficacy of atazanavir/ritonavir monotherapy was inferior as compared with atazanavir/ritonavir triple therapy. We also found that viral rebound under PI/r monotherapy occurred at low levels of viraemia and quickly reversed after reintroduction of NRTIs, allowing 82% of these patients to be in the study at week 96.

Virological failure was more frequent in the monotherapy arm while we observed many discontinuations due to the occurrence of AEs during the second year of follow-up in the triple-therapy arm. The 96 week efficacy rates of the MODAt study differed with those reported in previous studies evaluating other PI/r monotherapies.[1,2,7–10] However, differences in study design (such as the type and duration of the previous regimen) need to be considered as all these aspects clearly affect the 96 week performance of the regimens under evaluation.

We obtained less favourable results in patients with HCV infection, which continued to suggest that atazanavir/ritonavir monotherapy might be more risky.[12]

After considering re-intensification = success treatment success was higher among patients on monotherapy than triple therapy. All patients who experienced a loss of virological suppression while on atazanavir/ritonavir monotherapy had no evidence of resistance mutations and were able to achieve and maintain

Table 1. Percentage change in lumbar spine and total proximal femur BMD at week 96 according to study treatment and baseline RANKL

	96 week percentage change in lumbar spine L1–L4 BMD				96 week percentage change in total proximal femur BMD			
	median (IQR)	crude mean (standard error)	adjusted mean[a] (standard error)	P^a	median (IQR)	crude mean (standard error)	adjusted mean[a] (standard error)	P^a
Study arm								
ATV/r monotherapy	0.83 (−0.30 to 2.39)	0.81 (0.74)	−0.94 (1.41)	0.759	1.30 (−0.65 to 2.67)	2.03 (1.20)	1.16 (1.01)	0.012
ATV/r+2 NRTIs	−0.81 (−3.21 to 1.83)	−0.68 (0.57)	−1.40 (1.52)	ref	−0.47 (−2.44 to 1.21)	−0.31 (0.65)	−1.64 (1.07)	ref
Baseline RANKL								
<32 pg/mL	−0.04 (−1.66 to 1.55)	0.02 (0.52)	−0.07 (1.36)	0.167	0.91 (−1.17 to 2.67)	1.15 (0.93)	0.59 (0.96)	0.128
≥32 pg/mL	−2.53 (−5.70 to 0.97)	−2.19 (1.30)	−2.27 (1.61)	ref	−0.63 (−3.93 to 1.13)	−0.18 (1.58)	−1.08 (1.12)	ref
ATV/r monotherapy and BL RANKL <32 pg/mL	0.51 (−0.60 to 1.83)	1.02 (0.90)	0.64 (1.57)	0.201	2.14 (−0.65 to 3.56)	3.42 (2.09)	1.23 (1.12)	0.003
ATV/r monotherapy and BL RANKL ≥32 pg/mL	−1.47 (−7.60 to 1.07)	−2.21 (2.01)	−2.52 (2.07)	0.850	0.48 (−1.60 to 0.68)	−0.13 (0.66)	1.09 (1.47)	0.024
ATV/r+2 NRTIs and BL RANKL <32 pg/mL	−0.57 (−2.61 to 1.55)	−0.64 (0.60)	−0.77 (1.53)	0.531	−0.21 (−1.66 to 1.06)	−0.33 (0.60)	−0.04 (1.08)	0.024
ATV/r+2 NRTIs and BL RANKL ≥32 pg/mL	−2.53 (−3.56 to −1.86)	−2.16 (1.84)	−2.03 (2.06)	ref	−3.09 (−4.88 to 1.42)	−0.21 (2.81)	−3.24 (1.43)	ref

ATV/r, atazanavir/ritonavir; BL, baseline.

[a]Adjusted for age, gender, BMI, smoking, HCV, vitamin D or calcium supplementation, baseline CD4+, baseline osteocalcin, baseline CTX-I, baseline vitamin D and baseline osteoprotegerin by multivariate linear regression.

viral suppression after reintroduction of NRTIs. This observation confirmed what was previously observed in lopinavir/ritonavir or darunavir/ritonavir monotherapy studies, showing that the NRTI reintroduction was a successful strategy preserving future treatment options.[1,13,14]

Atazanavir/ritonavir monotherapy was associated with a 96 week safety benefit: a lower incidence of AEs leading to discontinuation or grade 3–4 AEs occurred among patients on monotherapy compared with patients on triple therapy. These events mainly involved renal function indicating a significant role of tenofovir on the occurrence of these AEs.[15]

Consistent with other reports, we observed an increase in total cholesterol and LDL-cholesterol with a small but significant improvement in HDL-cholesterol, likely explained by the removal of tenofovir.[16] The amelioration of fasting glucose under atazanavir/ritonavir monotherapy might have been favoured by the removal of the two NRTIs, which, in turn, may be involved in the mechanisms favouring the development of glucose impairment and metabolic syndrome.[17]

The removal of tenofovir might also explain the mild improvement in the estimated glomerular filtration rate, serum phosphate and alkaline phosphatase, and the loss of BMD was less,[18] as observed in the atazanavir/ritonavir arm. Differences between arms in BMD loss could also be explained by plasma RANKL, a marker of bone turnover, as previously reported in other studies.[19,20]

One important limitation of this study relies on the limited statistical power of the analyses because of the fact that enrolment in the trial was prematurely stopped based on the interim analysis efficacy results.

In conclusion, the 96 week analyses suggested that long-term efficacy of atazanavir/ritonavir monotherapy was inferior as compared with atazanavir/ritonavir triple therapy. In the atazanavir/ritonavir monotherapy arm, reintroduction of nucleosides, as needed, was always effective with no new resistance mutation; monotherapy was also associated with a lower incidence of AEs and improvement in femur BMD.

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Author contributions

L. G., A. C., V. S. and A. L. provided scientific input into study design. A. B., G. C., A. D. M., F. M., A. A., A. D. B., S. R., G. G. and S. D. G. assisted in the enrolment and management of the patients. M. B. and D. G. performed bone and inflammatory biomarker tests. L. G. performed the statistical analyses and wrote the first draft of the manuscript. All the authors evaluated clinical data from the study and reviewed and edited the manuscript.

Supplementary data

Figures S1 and S2 and Tables S1 and S2 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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