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MODAt
Monotherapy Once a Day with Atazanavir/r

RANKL predicts 96-week BMD changes in ATV/r monotherapy: a MODAt trial sub-study

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OSPEDALE SAN RAFFAELE

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Background

No data on bone biomarkers and BMD changes in subjects treated with atazanavir/ritonavir (ATV/r) monotherapy are available.

This is a substudy of the MODAt trial[1] with the aim to evaluate the association between bone biomarkers and changes in BMD over 96 weeks in patients treated with ATV/r monotherapy vs ATV/r+2 N(t)RTIs.

Methods

MODAt (NCT01511809) is a multicentre, randomized, open-label, non-inferiority trial. Patients on ATV/r 300/100mg+ 2N(t)RTIs since≥48 weeks, virologically suppressed since≥24 weeks, were randomized to ATV/r-monotherapy or to maintain ATV/r+2N(t)RTIs. This sub-study included patients treated with either ATV/r triple therapy or monotherapy (with no re-intensification due to virological failure) who reached week 96 or prematurely discontinued with available BMD determinations and plasma samples at baseline, week 48 and week 96. Participants underwent standardized DXA scan and tested bone biomarkers (osteocalcin, vitamin D, RANKL, osteoprotegerin, CTX-I).

BMD, T-score and Z-score were measured at lumbar spine (L1-L4) and total proximal femur, low BMD for chronological age (LBCA), osteopenia and osteoporosis defined according to the International Society for Clinical Densitometry[2] and WHO criteria[3], respectively.

Bone biomarkers were evaluated as continuous variables or categorical variables, stratified according to their median value.

Results as median (interquartile range, IQR). Chi-square/Fisher exact test or Mann-Whitney test were used to compare groups. Linear regression was applied to evaluate the predictors [age, gender, body mass index (BMI), smoking, HCV, baseline CD4+, study-arm, vitamin D or calcium supplementation, BL values of osteocalcin, RANKL, vitamin D, osteoprotegerin, CTX-I] of 48- and 96-week percent changes in vertebral and total proximal femur BMD.

Results

Among the 103 patients enrolled in the MODAt trial, 69 subjects had available BMD data [29 patients on ATV/r monotherapy, 40 patients on ATV/r+2N(t)RTIs] as reported in **Figure 1.** Baseline characteristics according to study arm is reported in **Table 1**.

Median (IQR) percent changes in lumbar spine and femoral neck and total proximal femur BMD according to study arm is reported in **Figure 2**.

Patients treated with ATV/r monotherapy or ATV/r+2N(t)RTIs had a similar incidence of vertebral or femoral LBCA/osteopenia [ATV/r: 3 (10.3%); ATV/r+2N(t)RTIs: 6 (15.0%); p=0.724]. No incident osteoporosis observed in both arms during follow-up.

Among patients treated with ATV/r monotherapy, higher baseline values of RANKL(≥32 pg/mL) were associated with lower 48-week percent changes in L1-L4 BMD and in total proximal femur BMD (**Figure 3**); this effect tended to be observed also among patients on ATV/r+2N(t)RTIs, although it was not statistically significant. All the other bone biomarkers were not associated with % changes in BMD at week 48 or week 96 in both arms.

At multivariate analysis (**Table 2**), ATV/r monotherapy was associated with an increase in the 48- and 96-week % change in total proximal femur BMD [W48: β=+1.44 (0.83), p=0.025; W96: β=+1.16 (1.01), p=0.012] as compared to ATV/r+2N(t)RTIs. Femoral BMD increased among subjects on ATV/r monotherapy rather than on ATV/r+2N(t)RTIs or among patients with low BL RANKL(<32 vs ≥32 pg/mL) at week 48 [β=+2.44 (0.92), p=0.001] and at week 96 [β=+1.23 (1.12), p=0.003].

Figure 1. Patients distribution

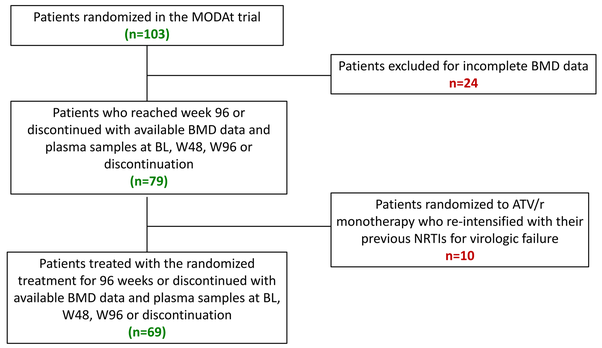
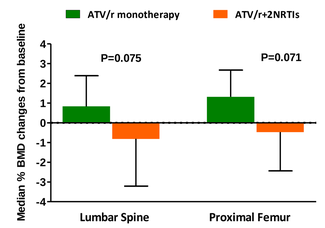


Table 1 – Baseline characteristics of study participants

	ATV/r (N=29)	ATV/r + 2N(t)RTIs (N=40)	P-value
Age, years	40.7 (34.7-45.0)	42.4 (34.7-46.8)	0.666
Males	22 (76%)	36 (90%)	0.182
White race	28 (97%)	37 (93%)	0.655
Smokers	12 (55%)	21 (60%)	0.785
BMI, kg/m^2	24.0 (22.0-25.1)	23.0 (21.5-26.3)	0.995
CD4 nadir, cells/µL	296 (230-363)	277 (180-348)	0.375
HCV co-infection	3 (10%)	9 (23%)	0.999
ART duration, months	23 (16-47)	22 (17-55)	0.589
Months on ATV/r + 2 NRTIs	19 (15-31)	20 (17-41)	0.271
TDF/FTC backbone	25 (86%)	35 (88%)	0.881
Vitamin D supplementation	7 (32%)	11 (31%)	0.998
CD4+, cells/µL	610 (464-783)	575 (396-726)	0.206
HIV-RNA<50 cp/mL, months	17 (10-42)	16 (12-49)	0.589
Lumbar spine BMD (g/cm^2)	0.975 (0.920-1.047)	1.016 (0.933-1.103)	0.359
Total proximal femur BMD (g/cm^2)	0.929 (0.874-0.973)	0.959 (0.871-1.024)	0.458
Osteocalcin (ng/mL)	20.4 (14.2-29.5)	25.2 (15.9-33.3)	0.342
CTX-I (ng/ml)	0.63 (0.44-0.82)	0.48 (0.35-0.69)	0.095
RANKL (pg/ml)	31 (31-61)	31 (31-42)	0.685
Vitamin D (nmol/L)	62 (52-113)	99 (59-142)	0.167
Osteoprotegerin (pg/ml)	988 (707-1395)	1046 (726-1418)	0.985

Results as median (IQR) or frequency (%)

Figure 2. 96-week univariate percent changes in lumbar spine and total proximal femur BMD according to study arm



Lumbar Spine BMD	ATV/r monotherapy [median (IQR)]	ATV/r + 2N(t)RTIs [median (IQR)]	p-value
Baseline (g/cm^2)	0.975 (0.920 ; 1.047)	1.016 (0.933; 1.103)	
Week 48 (g/cm^2)	0.998 (0.927; 1.072)	0.976 (0.898; 1.073)	
Week 96 (g/cm^2)	0.981 (0.912; 1.072)	1.003 (0.904; 1.071)	
% Changes between baseline and week 48	1.772 (-0.010; 3.998)	-0.988 (-2.270; 1.143)	0.002
% Changes between baseline and week 96	0.830 (-0.299; 2.388)	-0.811 (-3.207; 1.833)	0.075
Total proximal femur BMD	ATV/r monotheray	ATV/r + 2N(t)RTIs	p-value
Baseline (g/cm^2)	0.929 (0.874 ; 0.973)	0.959 (0.871 ; 1.024)	
Week 48 (g/cm^2)	0.959 (0.876; 0.996)	0.945 (0.861; 1.026)	
Week 96 (g/cm^2)	0.947 (0.884; 0.996)	0.929 (0.858; 1.030)	
% Changes between baseline and week 48	1.301 (0.020; 3.912)	-0.199 (-1.835; 1.738)	0.069
% Changes between baseline and week 96	1.321 (-0.649; 2.671)	-0.471 (-2.440; 1.209)	0.071

Figure 3. Median percent changes in lumbar spine and total proximal femur BMD according to study arm and baseline values of RANKL

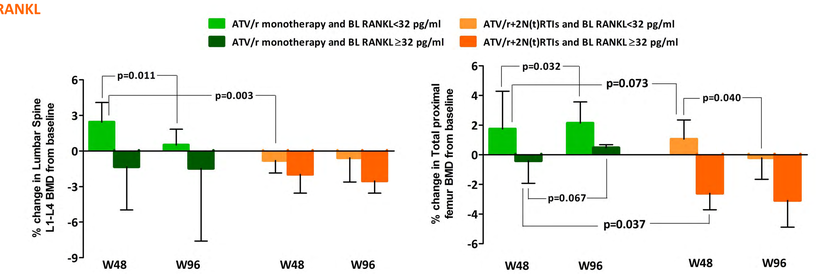


Table 2– Multivariate regression analysis: adjusted means of % change in BMD at week 48 and week 96 by site-specific DXA

	Lumbar Spine L1-L4 BMD				Total proximal femur BMD			
	Adjusted means § of % 48-week change in BMD [standard error]	p-value	Adjusted means§ of % 96-week change in BMD [standard error]	p-value	Adjusted means § of % 48-week change in BMD [standard error]	p-value	Adjusted means§ of % 96-week change in BMD [standard error]	p-value
Study Arm		0.252		0.759		0.025		0.012
ATV/r monotherapy	0.38 (1.22)		-0.94 (1.41)		1.44 (0.83)		1.16 (1.01)	
ATV/r + 2N(t)RTIs	-1.11 (1.31)		-1.40 (1.52)		-0.58 (0.88)		-1.64 (1.07)	
Baseline RANKL		0.026		0.167		0.011		0.128
<32pg/ml	1.21 (1.17)		-0.07 (1.36)		1.62 (0.79)		0.59 (0.96)	
≥32pg/ml	-1.93 (1.39)		-2.27 (1.61)		-0.76 (0.92)		-1.08 (1.12)	
ATV/r monotherapy and BL RANKL < 32 pg/ml	2.78 (1.36)	0.013	0.64 (1.57)	0.201	2.44 (0.92)	0.001	1.23 (1.12)	0.003
ATV/r monotherapy and BL RANKL ≥32 pg/ml	-2.01 (1.79)	0.941	-2.52 (2.07)	0.850	0.44 (1.21)	0.120	1.09 (1.47)	0.024
ATV/r + 2N(t)RTIs and BL RANKL < 32 pg/ml	-0.37 (1.32)	0.394	-0.77 (1.53)	0.531	0.80 (0.89)	0.018	-0.04 (1.08)	0.024
ATV/r + 2N(t)RTIs and BL RANKL ≥32 pg/ml	-1.85 (1.78)	Ref	-2.03 (2.06)	Ref	-1.96 (1.17)	Ref	-3.24 (1.43)	Ref

§ adjusted for age, gender, body mass index, smoking, HCV, baseline CD4+, vitamin D or calcium supplementation, BL osteocalcin, BL CTX-I, BL vitamin D, BL osteoprotegerin

Discussion

Patients treated with ATV/r monotherapy for 96 weeks showed an increase in BMD, especially at the total proximal femur site. The benefit of ATV/r monotherapy was more evident in patients with low baseline values of RANKL. Monotherapy with ATV/r may be an option in patients on ATV/r+2N(t)RTIs with low BMD for chronological age/osteopenia or osteoporosis.

References

1. Castagna A, Spagnuolo V, Galli L, et al. Simplification to atazanavir/ritonavir monotherapy for HIV-1 treated subjects on virological suppression: the MODAt trial. AIDS, 2014; 28(15):2269-79.

2. Schousboe JT, Sheperd JA, Bilezikian JP et al. 2013 Executive Summary of the 2013 ISCD Position Development Conference on Bone Densitometry. JCD;16(4):455-467

3. Kanis JA on behalf of WHO Scientific group: Assessment of osteoporosis at the primary health care level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK.

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