Similar neurocognitive performance in patients on ATV/r monotherapy vs triple therapy

MODAt
Monotherapy Once a Day with Atazanavir/r

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BACKGROUND

It has been hypothesized that patients receiving antiretroviral regimens characterized by poor central nervous system penetration effectiveness might have higher risk of HIV-associated neurocognitive disorders [1-3]. The aim of the study was to evaluate if neurocognitive performance (NP) might be different between patients with undetectable viral load treated with atazanavir/ritonavir monotherapy compared to those receiving ATV/r triple therapy for at least 96 weeks.

METHODS

MODAt (NCT01511809) is a multicentric, randomized, open-label, non-inferiority trial [4]. Patients on atazanavir/ritonavir (ATV/r) 300/100mg+2 N(t)RTIs since≥48 weeks, virologically suppressed since≥24 weeks, were randomized to ATV/r (Arm A) or to maintain ATV/r+2N(t)RTIs (Arm B).

Patients treated with either ATV/r triple therapy or monotherapy (with no re-intensification due to virological failure) who reached week 48 (Arm A: n=36; Arm B: n=44) and, if not discontinued, week 96 (Arm A: n=27; Arm B: n=32), with available neuropsychological evaluations at baseline (BL), week 48 and week 96 were included in this analysis.

Eight NP tests assessed multiple cognitive domains including attention/concentration (Digit Symbol [DS]), learning/memory (Rey Auditory Verbal Learning Test [RAVLT], Rey Recall [RAVLT rec]); psychomotor speed (Trail Making Test–Part A [TMTA], Grooved Pegboard [GP]), executive functioning (TMT–Part B [TMTB]), language (Semantic [SF] and Phonemic fluency [PF]).

Raw scores were transformed to z-scores using normative data of the Italian population adjusted for age, sex and education. Summary z-scores (NPZ-8) were calculated by averaging z-scores of the 8 NP tests; z-scores were also averaged by cognitive domain. Neurocognitive Impairment (NCI) was defined if scores were below ≥1 standard deviation (SD) normative means in ≥2 domains [5].

Depression was assessed by the CES-D scale, used both as a continuous variable or as a three-class variable [6]. Results are expressed as median (interquartile range). ANOVA for repeated measures and McNemar's test were applied in the longitudinal analyses.

RESULTS

Sixty-five patients had data on neuropsychological tests at BL and week 48 [Arm A=28 (78%), Arm B=37 (84%)]: 88% males; age, 40 (35-46) years; education, 13 (12-15) years; duration of HIV-infection, 5 (2-7) years; CD4+ nadir, 293 (224-388) cells/µL; BL CD4+, 610 (431-774) cells/µL, pre-ART HIV-RNA 4.67 (4-5.26) log10cp/mL; HCV co-infection (15%); none with AIDS diagnosis. No differences between the two arms with regard to BL demographic, clinical or laboratory characteristics (Table1). Fifty-three patients reached week 96 (Arm A=27, Arm B=26).

Baseline NP findings were similar between the two arms with the exception of TMT-B scores that were worse in arm B compared to arm A (Table 2). At baseline, CES-D score was abnormal (score>23) in 11 (17%) pts, borderline (score: 17-23) in 10 (15%) pts, with no significant changes of these proportions during follow-up (Figure 1). NP scores improved significantly over 96 weeks in five of the eight NP tests (Figure 2) with no trend differences between arms. The proportion of patients with NCI dropped from 66% at BL to 45% at W96 with no differences between arms (Figure 3).

Mean (SD) NPZ-8 scores improved during follow-up and were similar between arms at all time-points [Arm A vs B at BL: -0.02 (0.64) vs -0.15 (0.52), p=0.353; Arm A vs B at W48: 0.33 (0.67) vs 0.12 (0.57), p=0.194; Arm A vs B at W96: 0.31 (0.58) vs 0.25 (0.55), p=0.742]. Neurocognitive z-scores by ability domain and study arm are reported in Figure 4.

CONCLUSIONS

In subjects successfully treated for 96 weeks, neurocognitive performance was found to be similar between patients treated with ATV/r monotherapy compared to those receiving ATV/r triple therapy. The global neurocognitive performance similarly improved in both arms during follow-up, especially in the domains of attention, memory and language; a learning effect can't be excluded as a potential explanation for improvement. These results, although limited by the small number of patients, seem to reassure about the neurocognitive performance associated with antiretroviral regimens that might be characterized by poor central nervous system penetration or effectiveness, in patients with stable viral suppression.

Table 1 – Baseline demographic and clinical charactheristics

	ATV/r monotherapy N=28	ATV/r + 2N(t)RTIs N=37	P-value
Age	40 (36-46)	41 (33-46)	0.900[a]
Male gender	25 (89%)	32 (87%)	0.998[b]
Years of HIV infection	5 (2.5-7)	4 (2-7)	0.905[a]
CD4+ (cells/µL) nadir	290(229-386)	293 (199-388)	0.726[a]
Pre-ART HIV-RNA (log10 cp/mL)	4.8 (4.4-5.3)	4.5 (3.9-5.0)	0.158[a]
CD4+ (cells/µL)	627 (463-811)	559 (384-743)	0.292[a]
HCV infection	4 (14%)	6 (16%)	0.999[b]
Duration of current ART (months)	23.1 (15.4-54.0)	21.0 (17.6-45.5)	0.890[a]
Duration of HIV-RNA<50 cp/mL (months)	17.4 (9.6-48.7)	15.3 (11.9-40.1)	0.889[a]
Months of ATV/r treatment	18.4 (14.7-33.2)	19.8 (15.6-37.4)	0.371[a]

a by Wilcoxon rank-sum test b by chi-square or Fisher exact test

Table 2 – Baseline neuropsychological characteristics

	ATV/r monotherapy N=28	ATV/r + 2N(t)RTIs N=37	P-value[a]
Digit symbol	55 (42-64)	53 (40-60)	0.499
Rey Auditory Verbal Learning Test	42 (35-47)	40 (35-44)	0.474
Rey Recall	9 (7-11)	8 (6-10)	0.220
Trail Making Test–Part A	33(25-41)	34 (24-48)	0.555
Trail Making Test–Part B	75 (56-96)	86 (61-111)	***0.018***
Phonemic fluency	31 (26-43)	32 (20-37)	0.352
Semantic fluency	48 (37-53)	40 (34-48)	0.182
Grooved Pegboard [b]	65 (60-75)	64 (61-73)	0.612
CES-D scale	14 (7-19)	13 (5-23)	0.679

a by Wilcoxon rank-sum test b in the dominant hand

Figure 1 – The proportion of patients with impaired CES-D scores during follow-up

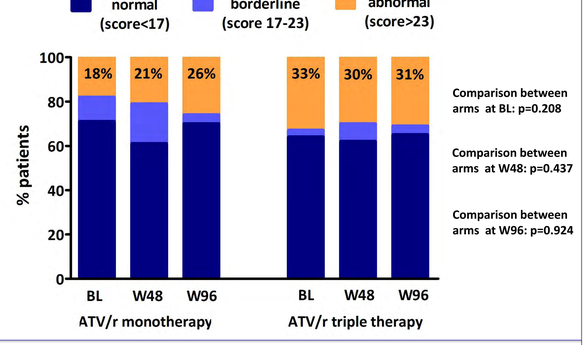


Figure 2 – Neuropsychological scores during 96-week follow-up

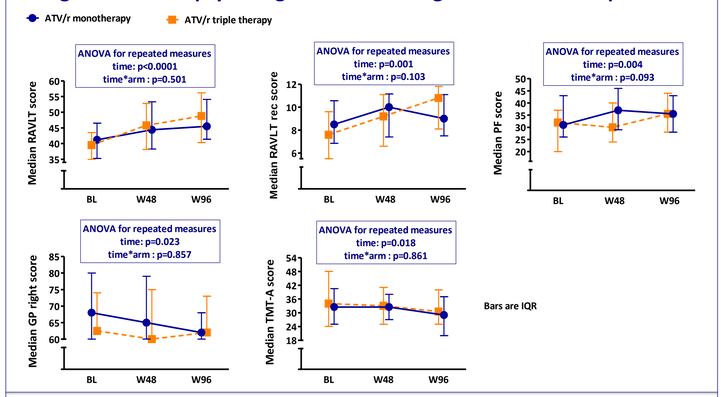


Figure 3 – The proportion of patients with Neurocognitive Impairment (NCI) during follow-up

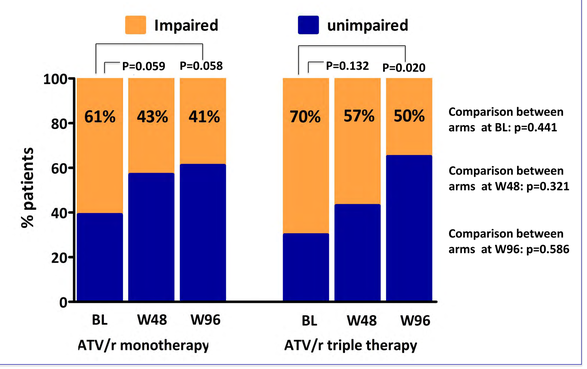
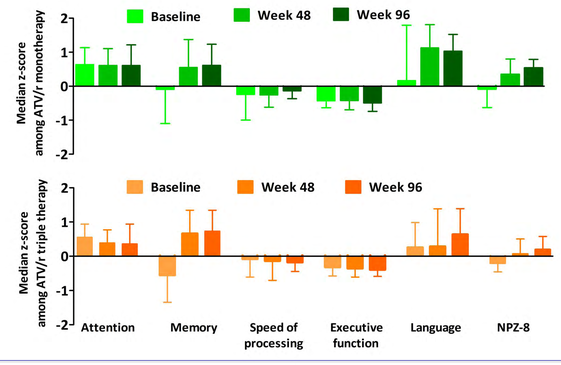


Figure 4 – Neurocognitive z-scores during follow-up by ability domain and study arm



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