THE EFFECTS OF NATALIZUMAB AND FINGOLIMOD ON CLINICAL AND MRI MEASURES IN RELAPSING-REMITTING MULTIPLE SCLEROSIS: A TWO-YEAR COMPARATIVE STUDY

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INTRODUCTION and PURPOSE

Natalizumab (NAT) and fingolimod (FTY) are second-line treatments approved for patients with active relapsing-remitting (RR) multiple sclerosis (MS) and they have been proven to be highly effective in reducing clinical relapses, disability progression and active lesion formation [1-10]. While pivotal trials have shown at two years the higher benefits of both FTY and NAT over placebo or interferon ß on clinical and MRI disease activity, no randomized clinical trial with head-to-head comparison has been conducted. Some observational studies have reported inconsistent results regarding differences on clinical and MRI activity between the two drugs [11-17].

Aims of this study were:

• To investigate the effects of these treatments in preventing clinical progression (relapses and disability);

• To combine conventional (T2 lesion volume [LV], T1 LV, cortical LV and gadolinium [Gd]-enhancing lesions) MRI measures and assessment of brain atrophy to monitor two-year changes of lesions, normal-appearing white matter (NAWM) and gray matter (GM) in MS patients who start treatment with NAT or FTY.

METHODS

•**Study design**. Monocentric, prospective, longitudinal, open-label, non-randomized study.

•**Inclusion criteria**. (a) RRMS starting treatment with FTY or NAT, according to Italian Medicine Agency (AIFA) criteria; (b) Age ≥ 18 and ≤ 60 years; (c) EDSS ≤ 6.0; (d) Stable treatment from at least three months of other concomitant symptoms (e.g., fatigue, mood disturbances).

•**Esclusion criteria**. (a) Contraindications to MRI; (b) Other neurological or psychiatric diseases; (c) Major medical illnesses including renal, hepatic or cardiac disease, or diabetes mellitus; (d) Pregnancy or breastfeeding.

•**Subjects**. Fifty-four RRMS patients starting NAT (n=28) or FTY (n=26). All patients underwent neurological and MRI assessments before starting treatment (T0), after six months (M6), one year (Y1) and two years (Y2) (+/- 7 days).

•**Neurological evaluation**. Rating of (a) clinical relapses, (b) EDSS, and (c) disability progression (EDSS score increase ≥ 1.0, when EDSS score at T0 was < 6.0, or an EDSS score increase ≥ 0.5, when EDSS score at T0 was ≥6.0).

•**Brain MRI acquisition**. 3.0 Tesla scanner: (a) dual-echo turbo spin-echo (TSE), (b) 2D double inversion recovery (DIR), (c) 3D T1-weighted fast field echo (FFE), and (d) post-Gd T1-weighted scans.

•**MRI analysis**.

• Quantification of number of Gd-enhancing lesions at T0, M6, Y1 and Y2 (*Jim 6.0, Xinapse System*).

• Evaluation of number of new T2-hyperintense lesions, new T1-hypointense and new cortical lesions at M6, Y1 and Y2.

• Estimation of T2-hyperintense, T1-hypointense, and cortical LVs at T0, M6, Y1 and Y2 (*Jim 6.0, Xinapse System*).

• Definition of non-evidence of disease activity 3 (NEDA-3).

• Assessment of normalized brain volume (NBV), GM volume (GMV) and white matter volumes (WMV) and percentage brain volume change (PBVC) (*SIENAx* and *SIENA* softwares), after refilling of T1-hypointense lesions.

• Derivation of normalized deep GM nuclei and hippocampal volumes (*FIRST* software).

•Assessment of longitudinal changes in GMV, WMV, deep GM nuclei and hippocampal volumes as the percent change *vs* previous timepoints.

•**Statistical analysis**.

• Mann-Whitney and Chi Square Tests: between-group comparisons of demographic, clinical, conventional and quantitative MRI measures at T0.

• Wilcoxon Signed Ranks Test, Mann-Whitney and Chi Square Tests: within-group and between-group comparisons of longitudinal modifications of clinical, conventional and quantitative MRI measures.

RESULTS

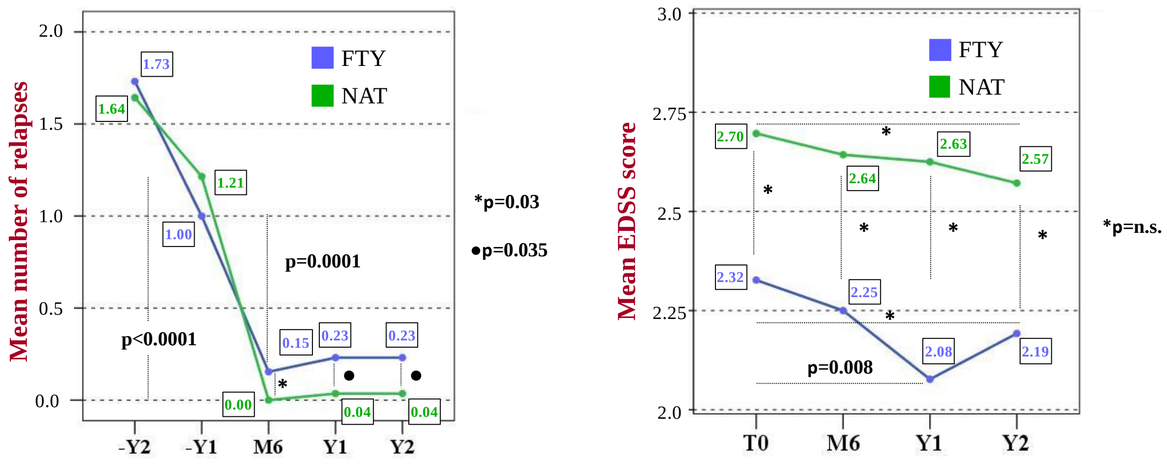
Clinical findings at T0. **Table 1** shows the main baseline demographic and clinical characteristics of MS patients.

Demographic and clinical variables		FTY (n=26)	NAT (n=28)	p value
Women/Men		16/10	17/11	0.95^
Mean age (SD) [years]		36.7 (9.3)	37.8 (9.9)	0.81*
Mean education (SD) [years]		13.7 (3.1)	13.6 (3.0)	0.91*
Mean disease duration (SD) [years]		10.9 (6.6)	9.7 (7.0)	0.49*
Median EDSS score (range)		2.0 (1.0-5.5)	2.0 (1.0-6.0)	0.32*
Mean number of relapses in the previous year (SD)		1.00 (0.8)	1.21 (0.8)	0.24*
Mean number of relapses in the previous two years (SD)		1.73 (1.2)	1.64 (1.1)	0.93*
Last treatment before recruitment (%)	• None	0 (0.0%)	4 (14.3%)	**0.02^**
	• Immunomodulants	19 (73.1%)	21 (75.0%)	
	• FTY	0 (0.0%)	2 (7.1%)	
	• NAT	6 (23.1%)	0 (0.0%)	
	• immunosuppressants	1 (3.8%)	1 (3.6%)	

^=Chi-Square Test

*=Mann-Whitney Test

Clinical evolution. **Figure 1** shows the modifications of clinical measures of MS patients during the follow-up.



- Lower number of clinical relapses after treatment start (p=0.0001 for FTY; p<0.0001 for NAT) and in NAT *vs* FTY at M6 (p=0.03), Y1 (p=0.035) and Y2 (p=0.03);
- Higher number of relapse-free patients in NAT *vs* FTY at M6 (100% *vs* 84.6%), Y1 (96.4% *vs* 76.9%) and Y2 (96.4% *vs* 76.9%) (p=0.03 for all comparisons);
- Improvement of EDSS score in FTY at Y1 (2.5 *vs* 2.0, p=0.008).
- No difference in the number of MS patients without disability progression at Y2 (96.2% in FTY *vs* 92.9% in NAT, p=0.6).

MRI findings at T0. **Table 2** shows the main baseline MRI characteristics of MS patients.

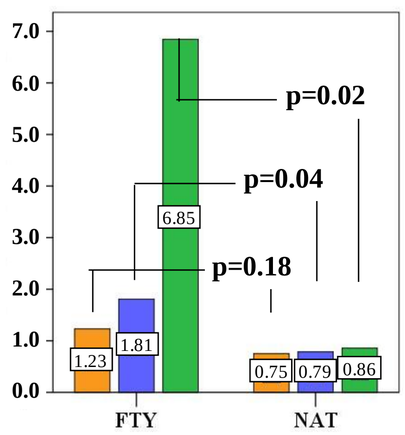
MRI variables	FTY (n=26)	NAT (n=28)	p value
Mean T2-hyperintense LV (SD) [ml]	9.1 (8.7)	9.7 (11.7)	0.57*
Mean T1-hypointense LV (SD) [ml]	5.9 (5.7)	6.6 (8.0)	0.65*
Median Gd-enhancing lesion number (range)	0 (0-3)	0 (0-2)	0.58*
Mean Gd-enhancing LV (SD) [ml]	0.02 (0.05)	0.02 (0.05)	0.46*
Number (%) of patients free of Gd-enhancing lesions	21 (80.8%)	20 (71.4%)	0.42^
Mean Cortical LV (SD) [ml]	0.16 (0.20)	0.10 (0.17)	0.17*
Mean NBV (SD) [ml]	1518 (97)	1521 (110)	0.67*
Mean GMV (SD) [ml]	702 (70)	703 (77)	0.70*
Mean WMV (SD) [ml]	816 (44)	817 (50)	0.72*
Mean normalized deep GM nuclei (SD) [ml]	23.9 (2.5)	24.4 (2.6)	0.44*
Mean normalized thalamic volume (SD) [ml]	9.6 (1.0)	9.9 (1.1)	0.20*
Mean normalized caudate volume (SD) [ml]	4.2 (0.6)	4.4 (0.6)	0.52*
Mean normalized putamen volume (SD) [ml]	5.7 (0.8)	5.8 (0.7)	0.49*
Mean normalized globus pallidus volume (SD) [ml]	2.1 (0.3)	2.1 (0.3)	0.22*
Mean normalized hippocampal volume (SD) [ml]	4.7 (0.5)	4.6 (0.6)	0.41*
Mean normalized amygdala volume (SD) [ml]	1.7 (0.2)	1.7 (0.2)	0.95*
Mean normalized accumbens volume (SD) [ml]	0.5 (0.1)	0.5 (0.1)	0.57*

^=Chi-Square Test

*=Mann-Whitney Test

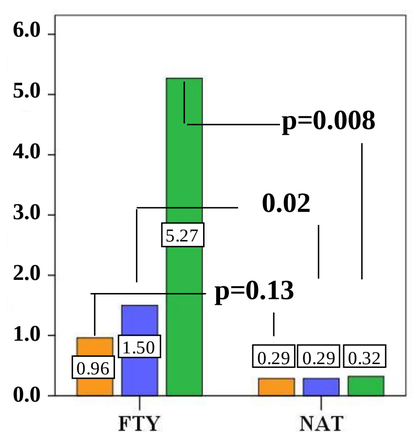
MRI evolution. **Figure 2** shows the longitudinal accumulation of new T2-hyperintense and T1-hypointense lesions and the modifications of T2-hyperintense and T1-hypointense LVs during the follow-up.

Mean number of new T2 lesions

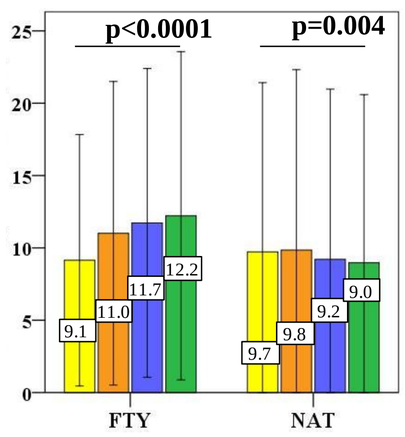


M6 *vs* T0
Y1 *vs* T0
Y2 *vs* T0

Mean number of new T1 lesions

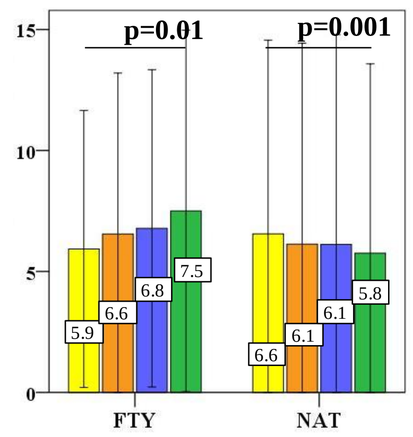


Mean T2 LV [ml]



T0
M6
Y1
Y2

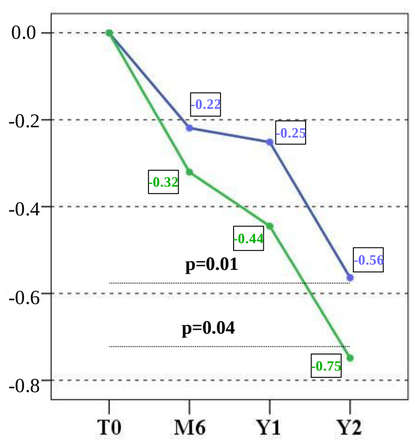
Mean T1 LV [ml]



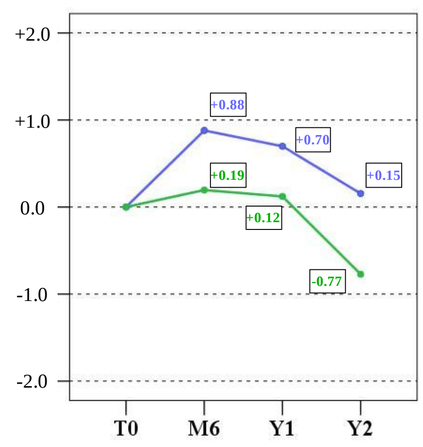
- Higher number of MS patients free from new T2-hyperintense lesions in NAT *vs* FTY group at Y1 (71.4% *vs* 38.5%, p=0.01) and Y2 (67.9% *vs* 34.6%, p=0.02).
- Higher number of MS patients free from new T1-hypointense lesions in NAT *vs* FTY group at Y1 (78.6% *vs* 50.0%, p=0.03) and Y2 (75.0% *vs* 46.2%, p=0.03).
- No difference in the number of MS patients free from Gd-enhancing lesions and new cortical lesions at the follow-up.
- Significant increase of T2-hyperintense LV (p<0.0001) and T1-hypointense LV (p=0.01) at Y2 in FTY patients.
- Significant decrease of T2-hyperintense LV (p=0.004) and T1-hypointense LV (p=0.001) at Y2 in NAT patients.
- Significant decrease of cortical LV over time in FTY patients (p values ranging from 0.0001 to 0.007).
- Significant differences between FTY and NAT patients in the longitudinal changes of T2-hyperintense and T1-hypointense LV (p<0.0001 for all comparisons) and in cortical LV at Y1 (p=0.01).
- Higher proportion of NEDA-3 patients in NAT *vs* FTY at Y1 (57.1% *vs* 30.8%, p=0.05) and Y2 (57.1% *vs* 26.9%, p=0.03).

- **Figure 3** shows the evolution of PBVC, percent GMV and percent WMV changes during the follow-up.

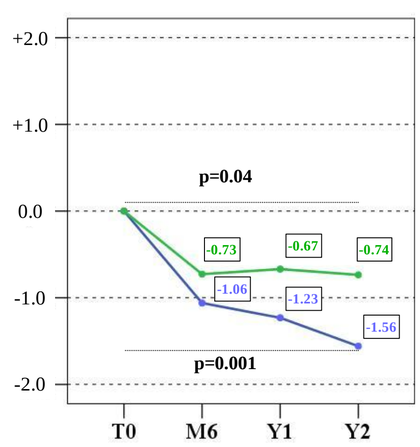
PBVC *vs* T0



GMV change *vs* T0



WMV change *vs* T0



FTY NAT

- Progression of deep GM atrophy in both groups at Y2 *vs* T0 (-1.40%, p=0.007 for FTY; -1.01%, p=0.01 for NAT).
- Progression of thalamic atrophy in both groups at Y1 *vs* T0 (-0.74%, p=0.002 for FTY; -0.87%, p=0.03 for NAT), and at Y2 *vs* T0 in NAT group (-1.09%, p=0.04).
- Progression of caudate atrophy in FTY group at Y2 *vs* T0 (-2.44%, p=0.01) and of globus pallidus in both groups at Y2 *vs* T0 (-2.35%, p=0.005 for FTY; -1.78%, p=0.01 for NAT).
- No difference of global and regional rate of atrophy between the two study groups.

CONCLUSIONS

• FTY and NAT are highly effective in reducing clinical relapses and MRI activity and preventing disability progression after 2 years of treatment in RRMS, with a slight superiority of NAT.

•In NAT treated patients, T2, T1 and cortical LV remained stable or slightly decrease after 2 years, while FTY treated patients showed a modest, although significant, increase of T2 and T1 LV.

•The 2-year rate of global brain atrophy in NAT and FTY patients was close to that reported for healthy controls, suggesting a positive role of both drugs in preventing irreversible tissue loss.

•Deep GM atrophy occurred for both drugs after 2 years of treatment, while WM atrophy occurred for both drugs already at M6 and progressed at Y1 and Y2.

•The strong anti-inflammatory effects of NAT might promote a secondary neuroprotection through a reduction of further inflammatory processes and the development of a more favourable environment to enhance tissue recovery.

•FTY might reduce neuroinflammation and exert direct neuroprotective effects in different CNS cells, including oligodendrocytes, astrocytes, and neurons.

• Further studies with larger sample size and longer follow-up are warranted to confirm these results and to better understand the pathophysiologic mechanisms influencing the different clinical and MRI findings related to these treatments.

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