The effect of Gilenya on grey matter damage, both focal and diffuse, in RRMS patients

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INTRODUCTION

Despite the crucial role of **grey matter (GM)** damage in disability progression in **Multiple Sclerosis (MS)** [1,2], and the large amount of scientific publications on the efficacy of **Fingolimod (FTY720)** in MS, its effect on focal and diffuse GM pathology is **still controversial**.

AIM OF THE STUDY

Our study is aimed at **evaluating the efficacy of Fingolimod** in reducing/preventing the accumulation of focal and diffuse GM damage and in preserving the physical and cognitive functions over **2 years follow up**.

METHODS

108 patients were **enrolled** in this **2-year** longitudinal study:

37 patients treated with FTY
71 treatment-free

74 patients, currently followed at the MS Center of Verona, **completed** the study:

35 patients treated with FTY
39 treatment-free

Each patient underwent

- a **NEUROLOGICAL EXAMINATION** every 6 months
- a **3T MRI** (Geurts et al., 2011) at baseline (T0), and after 12 (T12) and 24 months (T24). The images were processed by MIPAV to detect the cortical lesion (CL) and by FreeSurfer to establish regional volumes and cortical thickness of several areas.

COGNITIVE TESTS (RAO A + Stroop) have been performed in 16 FTY treated patients, at T0 and at the end of the study (T24).

The accumulation of new CLs, the progression of regional atrophy and related cognitive dysfunctions were compared between treated and untreated patients.

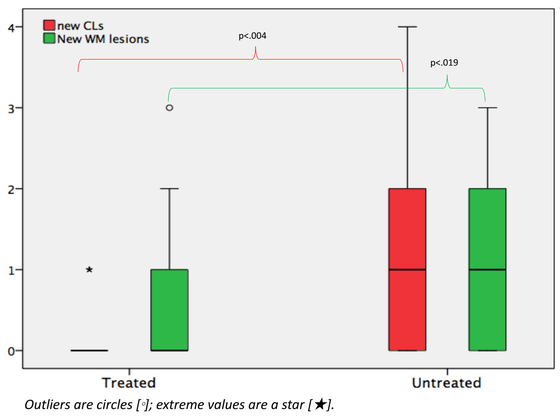
Demographical, clinical and MRI characteristics of the patients enrolled in the study

	FTY-treated group (n=35)	Untreated-group (n=39)
Gender	24F;11M	28F;12M
Age (years)	42.0 (9.2; 23.0-62.0)	32.0 (11.3; 16.0-61.0)
Disease duration (years)	11.0 (4.4; 3.0-23.0)	2.0 (1.2; 1.0-5.0)
EDSS score T0*	2.0 (1.0-5.0)	1.5 (0.0-2.5)
CLs number T0	6.9 (4.1; 0.0-19.0)	3.7 (4.0; 0.0-15.0)
WM lesions T0	11.3 (6.2; 4-31)	6.3 (5.4; 1.0-23-0)

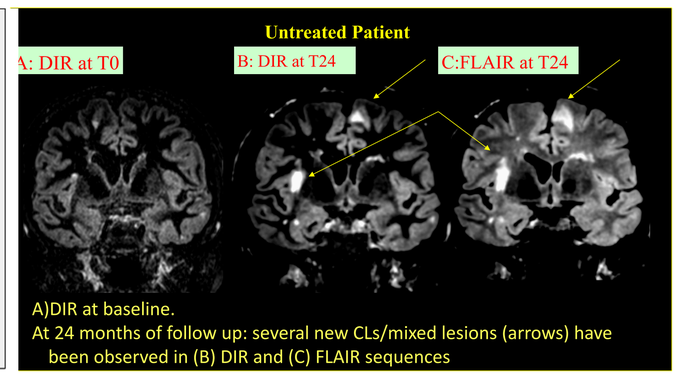
Data are reported as mean (standard deviation; range)
** Data are reported as median (range)*
EDSS= Expanded Disability Status Scale; WM: White Matter; CLs: Cortical Lesions detectable by DIR sequence

RESULTS

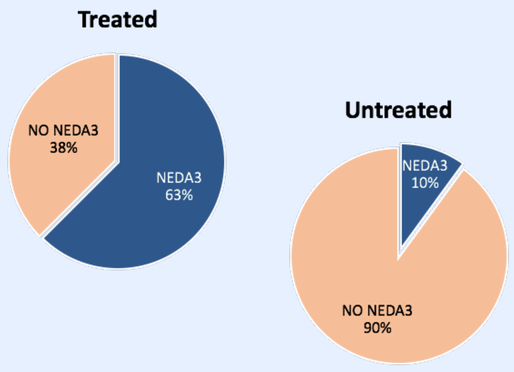
➪ **New CLs** or enlarged CLs were observed in 6 (17.1%) treated and 19 (48.7%) untreated patients (p=0.004), as well as the number of **new WM lesions** was lower in the treated (0.3± 0.7; 0.1-0.5) compared to untreated group (2.2±1.6; 1.6-2.7; p<0.001).



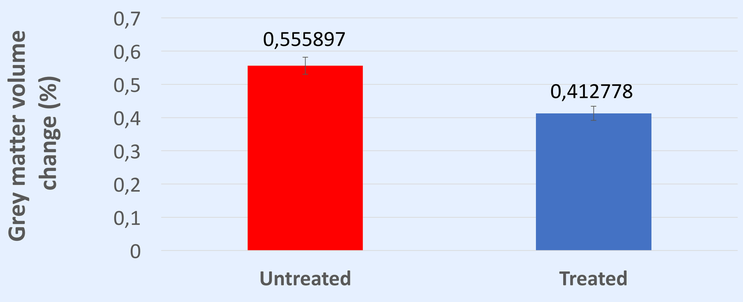
Outliers are circles [○]; extreme values are a star [★].



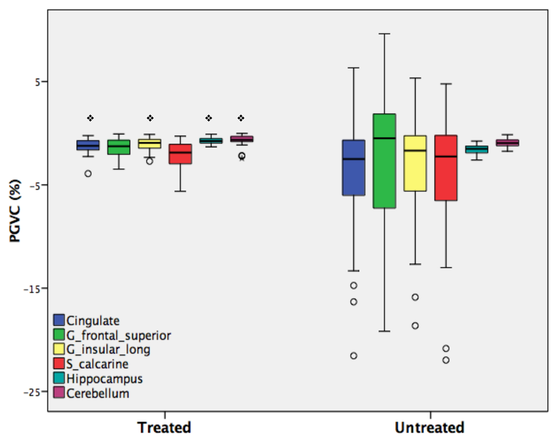
➪ The number of **NEDA-3** ('no evidence of disease activity') patients was significantly higher in the treated group (**62.5%**) compared to untreated group (**10.0%**) (p<0.001).

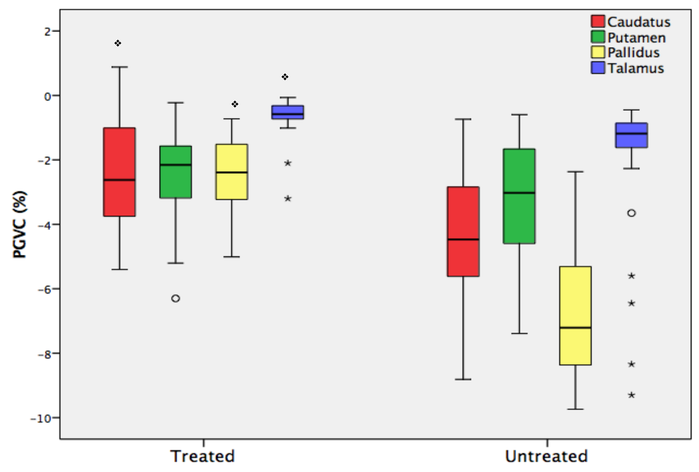


➪ The percentage of **grey matter volume change** (**PGVC**), was significantly lower in the treated compared to untreated group. (0.41% ± 0.12% vs. 0.56% ± 0.16%; *p<0.001*).



➪ Freesurfer analysis revealed that the treated group at T24 had less **VOLUME LOSS** in: thalamus, caudatus, globus pallidus and in hippocampus (p<0.001); significant difference has been found also in cingulate cortex, cerebellum and insular-long gyrus (p< 0.05).

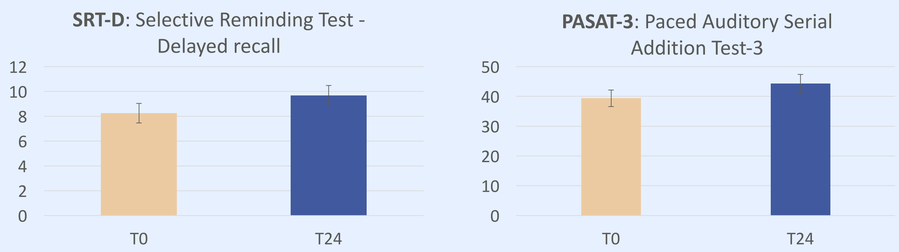




[❖] significant difference; *Outliers are circles [○]; extreme values are a star [★].*

➪ The **COGNITIVE TESTS** which significantly differed between T0 and T1 were

SRT-D (p < 0.007) and PASAT-3 (p < 0.001).



DISCUSSION

Several clinical trials have shown that FTY720 had both immunomodulatory and neuroprotective effect[3,4].

The **immunomodulatory** effect (compositional change of the peripheral blood cells and severe lymphopenia)[5] of the drug might reduce the number of inflammatory cells migrating into the CNS and, therefore, might explain its ability in reducing the accumulation of new CLs beyond the new WM lesions) which are known to be the result of an inflammatory autoimmune process[6].

On the other hand, the **neuroprotective** effect of FTY720 is confirmed by the lower total and regional GM volume loss of the treated group compared to the untreated group. FTY720 may exert such neuroprotective effect both in an *indirect* way through its main action on peripheral lymphocytes reducing the inflammatory response[5] and in a *direct* way, crossing the blood-brain barrier and exerting a direct effect on S1PR subtypes in the CNS cells (acting directly on the neuron's receptors, or through astrocytes and oligodendrocytes)[7-10].

From the **clinical** point of view, in line with previous studies[3,4], our results confirmed that FTY720 was able to reduce the number of relapses and the accumulation of irreversible disability (EDSS change) and, as a consequence, to increase the number of NEDA-3 patients. Moreover, the NEDA-3 usually does not take into account **cognitive** dysfunction[11], especially of learning and memory functions, which is a frequent feature of MS and that can be detected from the earliest stages of the disease[12]. For such reason, neuropsychological assessment was performed, according to recent indications claiming that also the absence of any change in the cognitive status should be required to speak of NEDA. Our results suggest that the effect of FTY720 had also a positive rebound effect on cognitive functioning.

Literature

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