Effect of glatiramer acetate on cerebral gray matter pathology progression in patients with relapsing-remitting multiple sclerosis: a 2-year monocenter study

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Background

Despite several evidences suggested the relevant contribution of grey matter (GM) damage to the long-term disability in multiple sclerosis (MS), no conclusive data about the "neuroprotective" effect of glatiramer acetate (GA) are available.

Objectives

This study proposes to compare the progression of cerebral gray matter (GM) pathology meant as a focal (cortical lesions) and diffuse (atrophy) damage in patients starting glatiramer acetate (GA) for relapsing-remitting multiple sclerosis (RRMS) to that of untreated patients.

Materials & Methods

Seventy-five patients currently followed at the Multiple Sclerosis Center of Neurology Section B were enrolled in this 2-year longitudinal study. Thirty-five were treated with GA and forty were untreated.

Study Design

All patients underwent 3 brain 3T-MRI at study entry (T_0), after 12 months (T_1) and 24 months (T_2) and neurological examination with EDSS evaluation every 6 months.

Image Acquisition Protocol

MRI sequences [Isotropic 3D DIR (1x1x1 mm), 3D-T1-MPRAGE (1x1x1 mm) and 3D-FLAIR (1x1x1 mm)] were acquired by Philips Achieva 3T MR Scanner with 8 head channel coil.

Image Analysis

At T_0, T_1 and T_2 , the number of new and pre-existing CLs was assessed region by region on DIR images by consensus of the two observers following the recent recommendations for CL scoring in patients with MS.

Cortical reconstruction and volumetric segmentation were performed at T_0 and at T_2 on a volumetric T1 weighted data set by means of the *longitudinal stream* included in the *Freesurfer image analysis suite*. The volume measurement of deep grey matter (DGM) and cerebellum with their respective volume changes as well as the regional cortical thickness changes in several cerebral areas were evaluated after 24 months

Statistical analysis

Differences among at T_0, T_1 and T_2 were assessed through analysis of variance . Since CLs and EDSS are not normally distributed, Mann-Whitney tests was used to compare populations with respect to their CL number, EDSS and EDSS change.

Results

Sixty-nine patients, of which thirty in therapy with GA, completed the study.
At T1, the mean number of **new cortical lesions** was significantly lower in GA treated-group (0.9 ± 1.0, range 0-3) compared to patients on no-DMT (1.7 ± 1.0, range 0-4; $p < 0.05$). At T2, the mean number of new cortical lesions was lower (1.4 ± 1.3, range 0-5) in treated group than in the untreated group (2.9 ± 1.8, range 0-7; $p<0.001$) and a volume loss of **thalamus** (-0.5% ± 0.2% vs. -1.1% ± 0.4%; $p<0.001$), **globus pallidus** (-4.4% ± 3.1% vs. -8.2% ± 4.5%; $p< 0.001$), **hippocampus** (-0.7% ± 0.3% vs. -1.5% ± 0.5%; $p<0.001$) and **cerebellum** (-0.5% ± 0.3% vs. -0.9% ± 0.4%; $p<0.001$) was lower in the GA group. Furthermore, a more pronounced cortical thinning was observed in **cingulate gyrus**, **cuneus gyrus** and in **frontomarginal gyrus** of the untreated patients ($p<0.05$). Finally, in the overall groups, there was no statistically significant difference between groups in terms of EDSS.

Discussion

Our novel findings suggest that GA exerts its immunomodulatory/neuroprotective action in patients with RRMS even at the level of GM reducing the accumulation of CLs and slowing down the atrophy progression also on the DGM, whose changes observed in this type of patients are, probably, due to both focal demyelinating lesions and diffuse neuronal loss.
The findings of immunomodulatory and neuroprotective effects of GA, such as the ability to binding MHC-II molecules, switching T cells from pro-inflammatory Th1 cells to Th2 anti-inflammatory cells and secreting neurotrophic factor would confirm the inflammatory origin of CLs.
It seems reasonable, at least in part, to hypothesize that the ability of GA to offer protection from cortical atrophy progression may depend by reducing the accumulation of new CLs.

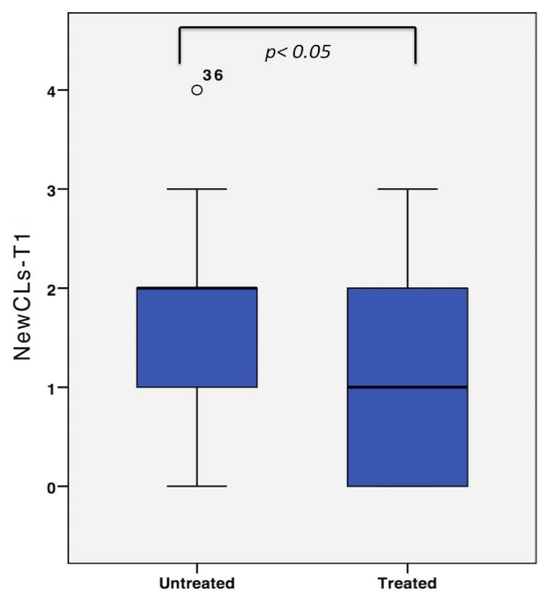
Conclusions

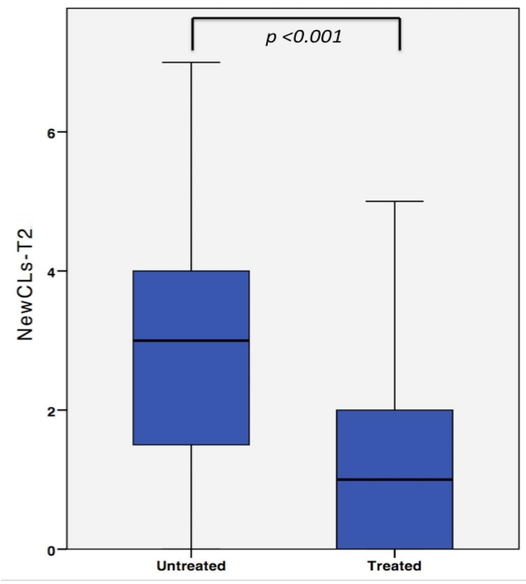
Despite a confirmation in a larger sample size is required, our results suggest a possible treatment effect of glatiramer acetate on gray matter pathology.
Compared to no treatment, institution of DMT reduced the accumulation of new cortical lesions and the rate of gray matter atrophy over 2 years. These findings also reinforce the idea of early therapy..

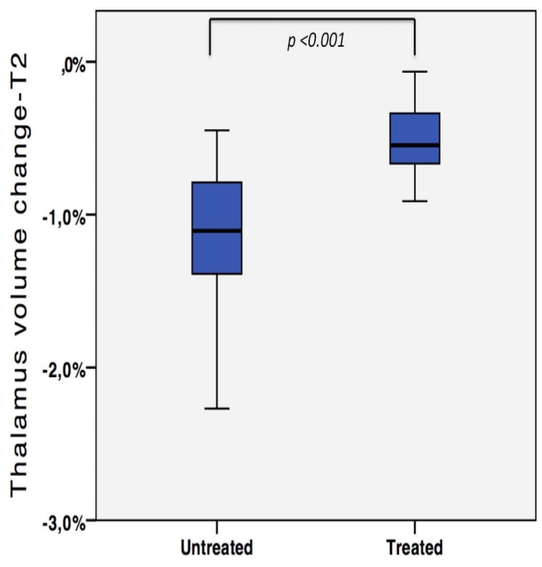
Demographical, clinical and MRI characteristics of the patients enrolled in the study

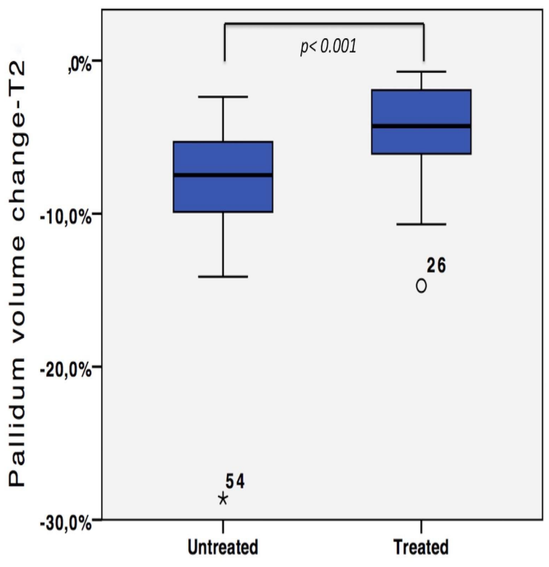
	GA treated-group (n=35)	Untreated-group (n=40)
Gender	27F;8M	28F;12M
Age (years)	38 (11; 19-63)	32 (11; 16-54)
Disease duration (years)	1.5 (1.2; 0-4)	1.7 (1.4; 0-5)
EDSS score	1.9 (0.7; 1-4)	1.8 (0.8; 1-4)
T2 WM lesions	9 (7.6; 2–36)	6.3 (5.4; 1-23)
CLs number	3.9 (4.4; 0-18)	3.7 (4; 0-15)

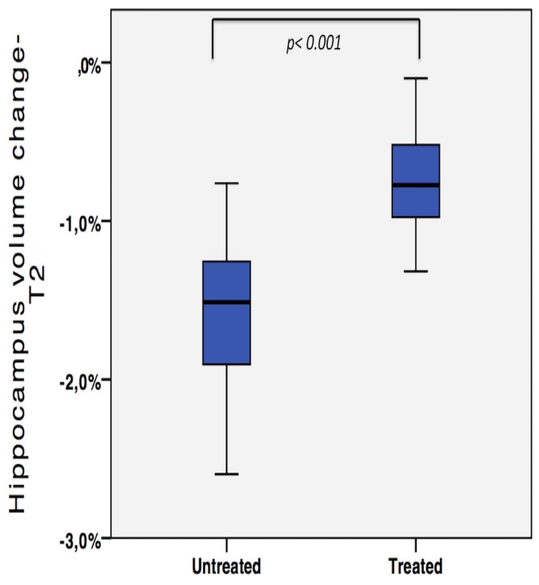
Data are reported as mean (standard deviation; range)
EDSS= Expanded Disability Status Scale; WM: White Matter; CLs: Cortical Lesions detectable by DIR sequence

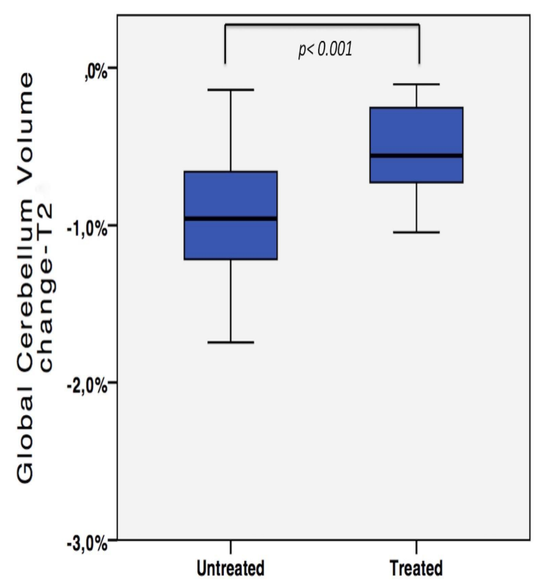












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