A Longitudinal, Frequent MRI Study Of Grey Matter Volume Changes In Active Relapsing-Remitting Multiple Sclerosis

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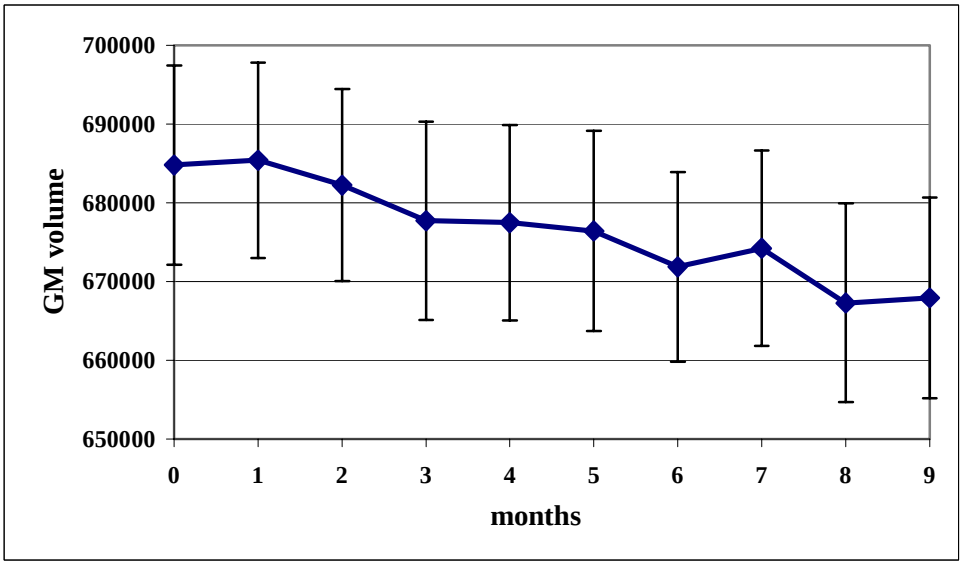
Objective: To investigate the patterns of short-term evolution of grey matter (GM) volume in a large sample of patients with relapsing-remitting (RR) multiple sclerosis (MS), by analysing the magnetic resonance imaging (MRI) dataset from the placebo arm of the European/Canadian glatiramer acetate (GA) trial.

Background: Several pieces of evidence suggest that conventional MRI-undetectable GM damage occurs soon after the clinical onset of MS. Little is known, however, about the time course of this damage, as well as about its relationship with other MRI-derived markers of MS evolution.

Design/Methods: The European/Canadian GA trial was a nine-month, double-blind, placebo-controlled study[1], where 239 RRMS patients were randomized to receive either 20 mg GA (n=119) or placebo (n=120) by daily subcutaneous injections. Dual echo, pre- and post-gadolinium (Gd) T1-weighted MRI scans of the brain were obtained at screening (to be included, patients had to have one or more enhancing lesions), baseline and every month during the follow-up period**.** Active lesions were counted and total T2-hyperintense and T1-hypointense lesion volumes (LV) measured using a semi-automated local thresholding technique. On T1-weighted images, normalized volumes of the whole brain tissue (WBT), white matter (WM) and grey matter (GM) were measured using a fully-automated method, the cross-sectional version of the Structural Imaging Evaluation of Normalized Atrophy (SIENA) software (SIENAX)[2]. Longitudinal percentage brain volume changes (PBVC) between baseline and study exit (month 9) scans were also estimated using SIENA.

Results: Data from 113/120 placebo patients were available for the present analysis (data loss was due to inadequate image quality for a reliable application of SIENA). Over the nine months of the study, the mean percentage change of GM and WM volumes were -2.30% (standard deviation [SD]: 4.78%) and 0.57% (SD: 4.86%), respectively. The mean PBVC at month 9 *vs.* baseline was -0.93% (SD: 1.16). Time-trend analysis (Figure) revealed that GM volume decrease was statistically significant ($p<0.001$). A random effect model correlation analysis showed that there was a significant relationship of GM decrease with both T2 LV and T1 LV increases over the same period of time (p values were 0.038 and 0.026, respectively).

Figure



Normalized GM volumes and 95% Confidence Intervals over the nine-month period of the study. Normalized GM volume is expressed in cubic millimeters.

Conclusions: This study shows that significant GM volume decrease occurs over short periods of time in patients with RRMS selected for MRI evidence of ongoing inflammatory activity. The progression of GM atrophy seems to depend, at least partially, upon the concomitant accumulation of MRI-visible white matter damage. Admittedly, these results deserve confirmation from other studies and have to be interpreted with caution, since the variability of the single time-point measurement of GM volume is fourfold higher than that ot the fully-automated assessment of two-timepoint whole brain volume changes.

References:

1. Comi G, Filippi M, Wolinsky JS, and the European/Canadian Glatiramer Acetate Study Group. Ann Neurol 2001;49:290-297.
2. Smith SM, Zhang Y, Jenkinson M, et al. NeuroImage 2002;17:479-489.