Effect of glatiramer acetate on MS lesions enhancing at different gadolinium doses

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Abstract—This baseline-vs-treatment study of 20 patients with relapsing-remitting MS investigated whether glatiramer acetate (GA) has a graduated effect on MS inflammatory activity, which was measured using monthly, standard, and triple dose gadolinium (Gd)-enhanced MRI. GA significantly reduced the mean numbers of enhancing lesions/patient/month on both standard dose and triple dose scans, without interactions with the Gd dose. GA is effective in reducing MS activity, independent of the severity of the MRI-detectable inflammatory process.

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Compared with a standard dose of gadolinium (Gd), a triple dose increases the harvest of enhancing MS lesions by 60 to 90%.[1,2] Hence, triple dose MRI enables us to reduce the number of patients and the duration of the follow-up needed to demonstrate treatment efficacy in MRI-monitored MS trials.[1,2]

Glatiramer acetate (GA) reduces the occurrence of standard dose enhancing lesions in relapsing-remitting MS (RRMS).[3,4]

This study investigated how GA treatment modifies MS inflammatory activity, as reflected by standard dose and triple dose Gd-enhanced scans.

Materials and methods. Patients were aged 18 to 50 years and had a diagnosis of RRMS, an Expanded Disability Status Scale (EDSS) score between 0.0 and 5.0, at least one relapse in the preceding 2 years, and one or more standard dose Gd-enhancing lesions on the screening scan. They also had to be relapse and steroid free in the 30 days before study initiation.

The study was a baseline-vs-treatment trial with single crossover. Treatment was GA (Copaxone, TEVA Pharmaceutical Industries Ltd., Israel), 20 mg daily by subcutaneous injections. Brain MRI scans were obtained every 28 ± 7 days for 2 periods of 5 months, before and 90 days after GA treatment. All patients had EDSS rating within 48

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Table 1 *Total and new gadolinium-enhancing lesions and new T2 lesions per patient at the individual MRI time points*

Period/visit month	Standard dose, total enhancing lesions	Triple dose, total enhancing lesions	Standard dose, new enhancing lesions	Triple dose, new enhancing lesions	New T2 lesions
Baseline					
−4	2.9 (2.1)/2.0/1–8	4.5 (2.8)/4.5/1–11			
−3	2.3 (2.2)/1.0/0–7	3.9 (3.4)/3.0/0–10	1.9 (2.2)/1.0/0–7	2.7 (3.0)/1.5/0–9	2.0 (2.3)/1.0/0–8
−2	3.4 (3.7)/2.0/0–10	4.9 (4.8)/3.0/0–14	2.9 (3.3)/2.0/0–10	3.5 (3.9)/2.0/0–13	2.2 (2.4)/2.0/0–8
−1	5.2 (8.3)/2.0/0–36	7.9 (10.7)/4.5/0–48	4.4 (6.9)/2.0/0–30	6.3 (8.7)/3.5/0–38	3.1 (3.9)/2.0/0–17
0	3.4 (4.5)/2.0/0–18	5.9 (6.2)/3.0/0–23	2.4 (3.1)/1.0/0–9	3.9 (4.3)/2.5/0–15	2.8 (3.4)/1.0/0–11
Treatment					
3	2.9 (3.2)/2.0/0–12	4.9 (5.2)/2.5/0–16			
4	2.1 (3.1)/1.0/0–14	3.8 (4.7)/2.0/0–18	1.5 (2.9)/1.0/0–13	2.5 (3.8)/1.0/0–15	1.3 (1.3)/1.0/0–5
5	1.4 (2.4)/1.0/0–10	2.5 (3.9)/1.0/0–14	0.8 (1.4)/0.0/0–5	1.4 (2.4)/1.0/0–9	0.5 (1.0)/0.0/0–4
6	1.2 (2.0)/0.0/0–7	1.7 (2.9)/1.0/0–10	0.8 (1.5)/0.0/0–6	1.2 (2.1)/0.0/0–9	0.9 (1.6)/0.0/0–6
7	0.7 (1.2)/0.0/0–4	2.4 (4.6)/1.0/0–18	0.4 (0.7)/0.0/0–2	1.6 (4.1)/0.0/0–18	0.5 (0.8)/0.0/0–2

Values are expressed as mean (SD)/median/range.

hours after each MRI session. In case of a relapse, treatment with IV methylprednisolone (1 gram per day for 3 days) was allowed. When this occurred, MRI was always scheduled either before treatment or 10 days after its end. No other immunologic treatment was allowed. The study was approved by the ethical committees of participating centers.

MRI acquisition was carried out using two 1.5 Tesla scanners (Milan and Genoa). The MRI examination was always split into two sessions, separated by 12 to 24 hours. During the first session, the following scans were performed: dual echo turbo spin-echo (repetition time [TR], echo time [TE] = 3300, 16/98 [Milan]; 2800, 30/90 [Genoa]); and precontrast and postcontrast (5 minutes after the injection of Gd) T1-weighted conventional spin-echo (TR, TE = 720, 14 [Milan]; 740, 12 [Genoa]). During the second session, dual echo and postcontrast T1-weighted scans were obtained with the same acquisition scheme of the first session. For all scans, 24 contiguous axial slices were acquired with 5-mm thickness, 192 to 256 × 256 matrix, and 220 to 250 mm^2 field of view.

The numbers of standard and triple dose total and new enhancing lesions and new T2 lesions were counted by two observers by consensus. Blinding to patient identity, scan order, treatment period, and Gd dose was kept during lesion identification except for the count of new lesions on serial scans, when the observers were unblinded to the scan order. Lesion volumes (LV) were assessed as previously described.[5]

The effect of Gd dose and treatment and their interaction on enhancing and new T2 lesions was evaluated using a negative binomial regression model.[6] Enhancing LV were log-transformed and their changes were analyzed using an analysis of variance model including Gd dose and treatment as covariates.

Results. Twenty-eight patients underwent an initial brain MRI and 20 of them (15 scanned in Milan and five in Genoa) who had at least one enhancing lesion on the standard dose scan were enrolled (mean age = 33.7, range: 20 to 46 years; median disease duration = 6.5, 1 to 18 years; median EDSS score = 1.5, range: 0.0 to 4.0). Eight relapses (seven patients) occurred during the baseline and three (three patients) during the treatment period. Ten steroid treatments were administered (baseline = 7, treatment = 3).

Table 1 reports the total and new Gd-enhancing and new T2 lesions per patient at the different time points. The mean numbers (SD) of total and new enhancing lesions/patient/month during the baseline period were 3.4 (3.1) and 2.9 (3.0) on standard dose scans, and 5.4 (4.3) and 4.1 (3.9) on triple dose scans. During treatment, the mean numbers of total and new enhancing lesions/patient/month were 1.7 (2.1) and 0.9 (1.3) on standard dose, and 3.3 (3.8) and 1.7 (2.0) on triple dose scans. The mean numbers of new T2 lesions/patient/month were 2.7 (2.7) before and 0.9 (0.8) during treatment. When comparing the two periods, the mean percentage changes (95% CI) in enhancing lesions/patient/month were −33% (−70%, +4%) for total standard dose lesions, −53% (−72%, −33%) for new standard dose lesions, −18% for total triple dose lesions (−60%, +24%), and −23% (−68%, +21%) for new triple dose lesions. The mean percentage change (95% CI) for new T2 lesions/patient/month was −37% (−0.1%, −75%). There were always more enhancing lesions on triple than on standard dose scans ($p < 0.0001$). GA treatment reduced the numbers of total and new standard and triple dose enhancing lesions and new T2 lesions/patient/month (all the comparisons: $p < 0.0001$). No interaction of treatment effect with Gd doses was found ($p = 0.17$ and 0.10 for total and new enhancing lesions). When the average numbers of active lesions per patient at each time point during the treatment period were compared with those during the baseline period, a significant reduction was found at month 4 for all variables (p values were 0.006 and 0.008 for total and new standard dose lesions, 0.001 for both total and new triple dose lesions, and 0.003 for new T2 lesions). This treatment effect persisted at all the subsequent time points ($p < 0.0001$ for all variables). At study entry, the median T2 LV was 10268 mm^3 (range: 2,341 to 3,3611 mm^3). The average enhancing LVs were higher on triple dose than on standard dose scans during both the study periods ($p = 0.02$) (table 2). GA reduced both stan-

Table 2 *Total standard dose and triple dose gadolinium-enhancing LV per patient per scan during the baseline and the treatment periods*

Period or difference	Standard dose scans	Triple dose scans
Baseline period, mm^3	523.2 (138.6)/351.0/21.8–2853.4	846.7 (184.9)/713.2/98.2–3637.4
Treatment period, mm^3	209.2 (71.8)/82.3/0.0–1201.0	348.1 (95.2)/145.5/0.0–1644.5
Absolute difference, mm^3	−313.9 (104.6)/−271.0/−1652.4–586.5	−498.6 (114.6)/−376.1/−1992.9–498.4
Difference, %	−46.4 (16.6)/−61.5/−100–+160	−48.1 (12.2)/−63.9/−100–+105

Values are expressed as mean (SEM)/median/range.

dard dose and triple dose enhancing LV ($p < 0.001$) (see table 2) and no interaction of treatment effect with Gd doses was found ($p = 0.47$).

Discussion. The current study shows that GA is effective in reducing MRI-measured activity in patients with RRMS, starting 4 months after treatment initiation. This agrees with findings from a previous placebo-controlled trial,[3] which is why we decided not to acquire MRI scans immediately after GA initiation. Such a study design enabled us to monitor accurately the time period when GA was expected to exert its effect more evidently, but conversely, it necessarily limited our ability to compare these results with those from studies with interferons (IFN), which are known to have a rapid effect in reducing active MS lesions.[7]

The absence of a significant interaction between Gd dose and treatment efficacy suggests that the effect of GA on enhancing lesions is homogeneous and may be not dependent on the severity of blood–brain barrier (BBB) disruption. Standard dose and triple dose MRI provide only indirect information on the degree of inflammation that accompanies active MS lesions. However, lesions enhancing only after triple dose are characterized by less increased BBB permeability and milder tissue damage than those enhancing after standard dose.[8] Because activation of blood-borne effector mononuclear cells, determining BBB disruption and Gd enhancement, is primarily driven by antigen-specific T cells, our data support previous evidence indicating that GA may act via inhibition of antigen-specific T cells rather than directly on effector cells.[9] A previous study showed that a low dose of IFNβ-1a had a twofold greater effect on reducing the number of triple dose lesions than on reducing the number of standard dose lesions.[7] This fits with the concept that IFNβ affects the BBB permeability in situ, either directly or by decreasing the release of proinflammatory cytokines.[10] Clearly, a comparison between two MS trials must always be done with caution and it is worth noting that in the IFNβ-1a trial,[7] patients were not selected based on baseline MRI activity and MRI monitoring during the treatment period was limited to 4 months immediately after the treatment initiation. In addition, IFNβ-1a was given at a dose that is known to be poorly effective in RRMS.

In this study, GA effect was slightly higher and appeared earlier than in a previous parallel-group, placebo-controlled trial.[3] This difference is likely the result of the different study designs. Whereas "regression-to-the-mean" may have enhanced the effect of GA in the current study, it cannot have a similar impact on findings from a parallel-group study. In addition, the sample size we studied was relatively small and patients had mildly disabling MS. These may be additional factors contributing to the partially discrepant results between these two studies. The trend toward a more pronounced treatment efficacy on standard than on triple dose lesions may be explained at least in part by the increased interpatient variability in the number of triple dose lesions.[2] CIs of the mean were indeed larger for triple dose lesions than for standard dose lesions, suggesting that the behavior of individual subjects may have influenced differently the overall lesion estimates.

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