Glatiramer acetate (Copaxone) treatment in relapsing–remitting MS

Quantitative MR assessment

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Article abstract—*Objective:* To evaluate the efficacy of glatiramer acetate (GA, Copaxone; Teva Pharmaceutical Industries, Ltd., Petah Tiqva, Israel) by MRI-based measures in patients with relapsing–remitting (RR) MS. *Methods:* Twenty-seven patients with clinically definite RR-MS were treated with either 20 mg of GA by daily subcutaneous self-injection (n = 14) or placebo (n = 13) for approximately 24 months. Axial dual-echo fast-spin-echo T2-weighted images and T1-weighted images before and after gadolinium (Gd) were acquired at 1.5 tesla and transferred into an image processing computer system. The main outcome measures were the number of Gd-enhanced T1 and T2 lesions and their volume as well as brain parenchyma volume. *Results:* The values of age, disease duration, Expanded Disability Status Scale (EDSS) score, the number of T1- and T2-weighted lesions, and their volume were similar between GA- and placebo-receiving groups at the entry of this study. There was a decrease in the number of T1-enhanced lesions ($p = 0.03$) and a significant percent annual decrease of their volume in GA recipients compared with those of placebo recipients. There were no significant differences between changes in the two groups in the number of T2 lesions and their volume. The loss of brain tissue was significantly smaller in the GA group compared with that of the placebo group. *Conclusions:* These results show that GA treatment may decrease both lesion inflammation and the rate of brain atrophy in RR-MS. **Key words:** Glatiramer acetate—Relapsing-remitting MS—Expanded Disability Status Scale score—MR—Volume measurement.

The traditional outcome measures in therapeutic tasks in MS are most often relapse frequency or progression in disability, as measured by standard disability indexes such as Expanded Disability Status Scale (EDSS) score.[1] Although these clinical markers still are emphasized as the primary outcome measures of definitive therapeutic or Phase III clinical trials,[2,3] neuroimaging techniques such as MRI may offer a more direct measure of pathologic changes within the CNS, and MRI is being used increasingly as an outcome criterion in many new treatments for MS in recent years.[4-6] Because MRI provides a more direct measure of the extent of pathologic changes, the potential advantages include the quantitative nature of the data, ability to detect subclinical activity, and sensitivity to the long-term subclinical accumulation of disease in the brain.[3] MRI criteria for MS treatment trials have been presented in the neurologic literatures in recent years[7] and typically are based on routine conventional or fast-spin-echo proton density (PD)- and T2-weighted as well as enhanced T1-weighted images. Recent advances in computer-assisted brain lesion load quantification[8-10] may help in accurately assessing the total volume of

signal abnormalities on either long or short repetition time (TR) images. More recently, studies of measurements of cerebellum,[11] spinal cord,[12] and cerebral atrophy[13] have shown a good correlation between the degree of atrophy and clinical disability. Their roles in monitoring in therapeutic trials, however, remain unknown.

Glatiramer acetate (GA, Copaxone; Teva Pharmaceutical Industries, Ltd., Petah Tiqva, Israel), previously called copolymer 1,[14] is the most recently approved drug in the United States for the treatment of MS.[15] Published results from a multicenter, double-masked, placebo-controlled trial showed its efficacy against relapsing-remitting (RR) MS in significantly decreasing the frequency of relapses by an average of 30%.[16,17] The work presented here reports the results of MRI studies performed on a cohort of patients at one site in the multicenter Phase III trial. We have quantitated both the changes in the volume of brain lesions and the absolute number of lesions over time based on gadolinium (Gd)-enhanced T1- and T2-weighted images. We have also quantitated the whole brain parenchyma volume to analyze the effect of treatment on the development of brain atrophy.

Materials and methods. *Patients.* The study design, patient enrollment criteria, baseline clinical and demographic data, and overall results of the multicenter Phase III trial were published previously.[16,17] The cohort enrolled at the University of Pennsylvania included 23 women and 4 men, ages 25 to 45. All had clinically definite RR-MS with disease duration of 1 to 17 years. Baseline EDSS ranged from 1.0 to 5.0. Fourteen subjects were randomized to receive active drug (GA, 20 mg subcutaneously daily), and 13 received placebo. Four placebo patients did not complete the entire 2-year studies but instead were on study for between 0.54 and 1.39 years. The reasons the patients cited for dropping out were unrelated to treatment-induced adverse effects and included movement to another state (1), excessive attention (2), and continued clinical signs (1). Study medication was supplied by Teva Pharmaceutical Industries, Ltd (Petah Tiqva, Israel) under a manufacturing protocol approved by the Institutional Review Board of the University of Pennsylvania, and informed consent was obtained from all patients before enrollment.

MR imaging and analysis. MR studies were performed at the scheduled study accompanied by masked clinical evaluation. All brain MRI scans during this trial period were performed at 1.5 T (General Electric, Milwaukee, WI) using a quadrature head coil. Three-millimeter contiguous, interleaved axial dual-echo fast-spin-echo (PD and T2) images were collected from all patients according to the following protocol: TR = 2,500 msec; echo time (TE) = 18/90 msec; echo train length = 8; 192×256 matrix; number of excitations = 1; field of view = 22 cm^2. The T1-weighted spin-echo (TR = 600 msec/TE = 27 msec) images were acquired before and after injection of Gd-DTPA at 0.1 mmol/kg with similar field of view and slice thickness to the dual-echo images.

All patient studies were transferred electronically to our medical image processing laboratory, where the total number and volume of T2 lesions and Gd-enhancing T1 (Gd-T1) lesions were computed. The associated image processing was performed using an internal version of the 3DVIEWNIX software system[18] on a Sun Sparc 20 (Sun Microsystems, Mountain View, CA) workstation. The algorithms are based on a theory of object definition in images that has been well described previously with very low intrareader and inter-reader variability.[19,20] Various aspects of the theory as well as the algorithms were described in detail elsewhere.[21] The brain parenchyma volume was also calculated using 3DVIEWNIX. The process begins with excluding the extracranial contents based on segmentation of fuzzy connected three-dimensional objects (gray matter, white matter, and CSF) to get the intracranial contents including brain parenchyma and CSF.[19,20] An angle image of CSF is then produced from segmented T2- and PD-weighted data sets.[20] In brief, this technique creates a voxel-by-voxel image using the following formula: I_{angle} = $\tan^{-1}(I_{T2}/I_{PD})$, where I_{angle}, I_{T2}, and I_{PD} are the intensities of the corresponding voxels from the angle and from the T2- and PD-weighted images. The resulting angle image has relatively homogeneous CSF intensity values, which can be easily thresholded to produce a CSF-only image and volume. The total brain parenchyma image and volume are obtained by subtracting CSF image and vol-

method has been routinely used in our department for brain segmentation and has shown >99% reproducibility. The interoperator and intraoperator coefficient of variation for total T2 lesion volume in this system has been found to be $\leq 0.9\%$.[19,20] The 95% CI of the false-negative volume fraction (i.e., the volume of missed lesions as a fraction of the total volume of true lesions) has been 0% to -2.8%. For enhanced lesion assessment,[9] the system has no interoperator and intraoperator variations, with only 1 missed enhancing lesion of 38 true lesions.

Statistical analysis. The Mann–Whitney–Wilcoxon test was used to compare the two treatment groups with respect to the change per year in each of the outcome variables. The change in each outcome variable was computed as the last observation minus the baseline response so that negative values correspond to a decline in response over the course of the study. For outcome variables that were strictly positive at study onset, the yearly change in response is reported as a percentage of the baseline measurement. A Bonferroni correction for multiple hypothesis tests was used to ensure an overall type-I error rate no greater than 5% when comparing the two treatment groups. Specifically, with respect to each outcome variable, the treatment groups were declared significantly different at the 5% level only if the probability value for the relevant statistical test was $<0.05/6 = 0.0083$.

Results. All 27 patients were observed for a period of at least 6 months with a median time on study equal to 1.99 (range, 1.54 to 2.17) and 2.03 (range, 0.54 to 2.64) years in the GA and placebo groups, respectively. The demographics, clinical characteristics, and MRI measurements of the two treatment groups at the entry of this study are summarized in table 1. To determine the impact of group differences in these factors on our results, we repeated our primary group comparisons with respect to the outcome variables after including all baseline variables as covariates. The impact on our results was minimal; therefore, only the results of the adjusted analyses are presented here.

The annual changes in EDSS, brain parenchyma volume, as well as the T1 and T2 lesion number and volume are summarized in table 2. Clinical outcomes for our patient cohort differed from those of the study cohort as a whole in showing no significant reduction in relapse rate or change in EDSS around 2 years. There were 24 relapses in both the 14 GA-treated patients and the 13 placebo-treated patients. The mean percentage change of EDSS was 5.9% in the GA group and -1.3% in the placebo group ($p = 0.08$). There was a significant difference between GA- and placebo-treated groups with respect to the annual change in both brain parenchyma volume and Gd-T1 volume. Specifically, the placebo-treated patients exhibited a nearly threefold greater annual decline in brain volume than GA-treated patients. The Gd-T1 enhanced lesion number showed a decrease trend ($p = 0.03$) in the GA group compared with that of the placebo group after using Bonferroni correction for multiple hypothesis tests. No other difference between the two treatments was significant at an overall significance level of 5%.

Discussion. GA is a mixture of synthetic random polypeptides made from alanine, glutamic acid, lysine, and tyrosine[15] that has shown a clear benefit in

Table 1 *Baseline characteristics of GA- and placebo-treated patients with MS*

Characteristic	Mean		Median		SD		p Value*
	Placebo	GA	Placebo	GA	Placebo	GA	
Age, y	34.4	37.1	33.8	36.4	6.3	6.1	0.28
Disease duration, y	4.2	5.2	4.0	5.0	3.0	3.7	0.22
EDSS	2.4	3.0	2.5	3.0	0.8	1.0	0.13
Gd-T1 number	1.5	3.1	1.0	1.0	1.7	5.0	0.25
Gd-T1 volume (mm^3)	93.8	215.0	42.0	74.0	177.4	391.0	0.31
T2 number	28.7	21.3	17.0	22.0	12.8	22.1	0.30
T2 volume (mm^3)	8654.1	6521.2	6438.1	3610.0	6279.0	8678.0	0.48

* p Value is the significance level obtained from a Mann–Whitney test of the difference between the GA and placebo treatment groups.

GA = glatiramer acetate; EDSS = Expanded Disability Status Scale; Gd-T1 = gadolinium-enchancing lesion.

MS.[22,23] Clinical and laboratory-based studies suggest direct interference by GA with antigen (myelin basic protein) presentation by antigen-presenting cells to effector T lymphocytes and ultimately at least partial blocking of the putative demyelinating cascade.[24-26] In the aforementioned multicenter GA trial,[17] the therapeutic activity of GA showed a reduction of the mean relapse rate (>2 years) and a slower decline of EDSS in GA patients compared with placebo patients, although we failed to see a similar significant clinical benefit in our small cohort. However, the MRI analysis was not reported in the previous large multicenter GA trial. A recent MRI study[27] examined the effect of GA on MRI changes in 10 patients and showed the frequency of new Gd-enhancing lesions decreased during the treatment period compared with that of the pretreatment period. The study assessed lesion area instead of lesion volume and did not have a control group.

In our study, the MRI-based measurements showed that treatment with GA has a favorable impact on enhancing T1 lesions and whole brain parenchyma atrophy. The different change of T1-enhancing lesion volume (−83.5 mm^3 versus 147.5 mm^3, mean) and brain volume (−0.6% versus −1.8%, mean) was significantly different between GA-treated and placebo-treated patients with RR-MS. This MRI-based systematic study for evaluating the efficacy of a randomized, placebo-controlled GA trial in RR-MS objectively used a highly reliable brain and lesion volume quantitation technique that may provide insight into the events involved in lesion development and brain parenchyma loss in MS.

In MS, the lesions seen on MRI principally reflect a histopathologic spectrum including the presence edema, demyelination, remyelination, and inflammation. The two most commonly used MRI measures of MS lesions are the new lesions in Gd-enhanced T1-weighted images and the amount of abnormal brain tissue as seen in PD- and T2-weighted images. One of the early abnormalities believed to occur during the formation of the MS plaques is the breakdown of the blood–brain barrier, which can be detected by Gd-enhanced MR images.[28-31] It is believed that the systematic use of repeated Gd-enhanced scans can reveal a very high degree of activity in which there is a good correlation with clinical activity compared with the PD- and T2-weighted scans.[32,33] Recent data

Table 2 *Change per year from baseline to endpoint*

Measurements	Mean		Median		SD		p Value*
	Placebo	GA	Placebo	GA	Placebo	GA	
EDSS (%)	−1.3	5.9	0	8.6	11.3	20.6	0.08
Brain volume (%)	−1.8	−0.6	−1.6	−0.5	1.8	0.9	0.0078
Gd-T1 number	0.5	−1.2	0.5	−0.2	1.0	2.7	0.03
Gd-T1 volume	147.5	−83.5	50.6	−9.5	226.1	185.3	0.003
T2 number (%)	18.7	18.3	14.0	0.6	25.8	43.2	0.34
T2 volume (%)	16.8	53.0	8.9	19.8	26.7	76.3	0.51

* p Value is the significance level obtained from a Mann–Whitney test of the difference between the GA and placebo treatment groups.

have also suggested that the volume of tissue rather than the number of lesions might be a better criterion for evaluating the disease activity in MS.[34] In our study, there was a significant difference of annual change for Gd-T1 enhanced lesion volume between GA and placebo group, both when considering using Mann–Whitney–Wilcoxon test and using Bonferroni correction for multiple hypothesis tests. Our results confirmed the effect of GA on Gd-enhanced lesions observed by another group,[27] although the yearly change of the number of enhancing lesion did not reach significant difference between GA- and placebo-treated groups after using correction of multiple hypothesis tests. The effect of GA on Gd-T1 lesion volume may reflect short-term anti-inflammatory effects in improving the integrity of the blood–brain barrier in patients with RR-MS, however, whereas measures of brain parenchyma volume likely reflect largely irreversible tissue loss.

Changes in T2 lesion load have been used frequently to monitor clinical trials as the long-term progression measure in patients and likely reflect both reversible and irreversible pathologic change. Unlike enhancement, T2-weighted abnormalities may persist indefinitely and likely represent permanent focal myelin loss, gliosis, and some neuronal cell loss, as well as some reversible edema and inflammation.[35] However, T2 lesion number and T2 lesion volume may not reflect global parenchyma loss and global treatment effect. In our study, the number of T2 lesions and their volume between two treatment groups did not reach a significant difference, whereas the measures of whole brain parenchyma atrophy did. This may reflect the small sample size of our study, as well as the partially reversible nature of some T2 lesions. The mechanisms of the therapeutic benefits of GA in T1-enhanced and T2 lesion in patients with RR-MS are still unknown but may be similar to its effect of suppressing EAE in the acute phase.[36]

Brain atrophy has long been found in patients with MS.[37,38] Because of the multifocal nature of MS lesions dispersed throughout the entire brain, the relation between MR lesion load and clinical disability was shown to be variable and complex. Recently, quantitative brain parenchyma measurements have shown good correlation with disability measures.[13] We used a highly reliable brain segmentation technique to follow the treatment effects of GA and placebo. Preservation of brain parenchyma by a specific therapeutic regimen represents an important measure of treatment efficacy. We have shown a different percent change of brain volume (brain atrophy) in two treatment groups. Our data provide evidence that GA may slow progressive brain atrophy (i.e., cell loss) in RR-MS ($p = 0.0078$), even in these two small sample groups. Such precise, quantitative measures of brain volume may offer a more sensitive measure of drug efficacy in MS than currently used MR as-

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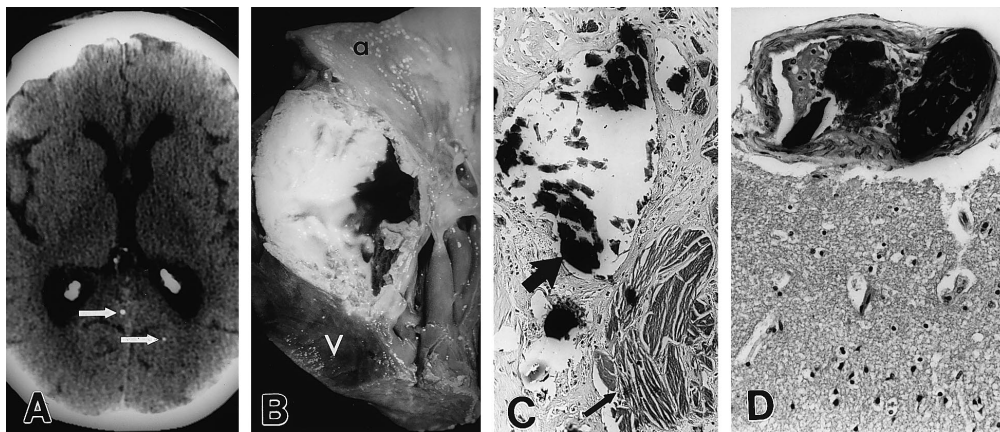
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Figure. (A) Punctate calcifications in brain CT scan (arrows). (B) Vertical section of heart with large MAC cavity between left atrium (a) and left ventricle (V). (C) H-E stain of mitral annulus wall embedded with dark spicules of calcium (thick arrow) and paler, amorphous substance (thin arrow). Original magnification ×100 before 96% reduction. (D) Embolic calcific material in subarachnoid artery, original magnification ×160 before 96% reduction, Luxol Fast Blue stain.

Mitral annulus calcareous brain emboli

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This 86-year-old woman came to the emergency room with 2 days of visual flashing lights and "floaters." Within hours, she developed myocardial infarction, right hemiparesis, back pain, and coma and died. Radiographs showed extensive mitral annular calcification (MAC) and multiple punctate calcifications in the brain. Autopsy showed erosion of a massive MAC with extrusion into the left atrium. Material identical to the MAC content was found in vessel lumens of all organs sampled except the lungs. Calcareous matter occluded multiple subarachnoid and brain parenchymal vessels.

Calcific embolization is regarded as a rare complication of temic embolization from MAC has been well documented pathologically but not radiologically. Previously, a small, calcific density on a brain CT scan was suggested to represent calcific embolus from the mitral valve, but without pathologic documentation.[1] Our case provides pathologic confirmation that the punctate calcifications in the brain images correspond to the fatal shower of calcific emboli. The exact incidence of calcific emboli from MAC is unknown. A suggested frequency of 11.3% indicates under-recognition and under-reporting of this complication.[2] This case illustrates that recognition of embolic calcifications on brain imaging enables antemortem diagnosis of MAC rupture.

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