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Effect of copolymer-1 on serial gadolinium-enhanced MRI in relapsing remitting multiple sclerosis

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Article abstract—We examined the effect of Copolymer-1 (Cop1) on magnetic resonance (MR) imaging changes in 10 patients with relapsing-remitting multiple sclerosis (RRMS). Monthly gadolinium (Gd)-enhanced MR imaging was performed for 9 to 27 months in the pretreatment period followed by 10 to 14 additional months during Cop1 treatment. MR images were evaluated by two radiologists (F.S. and R.C.P.) masked to the scan date. We found a 57% decrease in the frequency of new Gd-enhancing lesions and in the mean area/month of new Gd-enhancing lesions in the Cop1 treatment period compared with the pretreatment period (0.92 versus 2.20 lesions per month and 22 mm^2 versus 43 mm^2 area/month; $p = 0.1$, Wilcoxon signed rank test). Percentage change in lesion load area on T2-weighted images showed a decrease in the accumulation of lesion area during treatment, which was significant for the patient group with a longer pretreatment period ($p = 0.05$, Friedman test). These results demonstrate a reduction in the number of new Gd-enhancing lesions and in the lesion load during Cop1 treatment compared with the preceding period without therapy and are suggestive of an effect of Cop1 on MR abnormalities observed in multiple sclerosis.

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Magnetic resonance (MR) imaging is increasingly used in monitoring the clinical course of multiple sclerosis (MS) and assessing the therapeutic effects of promising treatments.[1,2] Although the relation between clinical and MR measures remains weak, a correlation between MR changes and clinical course has been demonstrated. There is a relation between exacerbation rate and occurrence of contrast enhancing lesions[3] and between disability (Expanded Disability Status Scale [EDSS]) and frequency of acute enhancing lesions.[4] Moreover, the total lesion load detected on T2-weighted images at MR examination correlates with clinical progression in monosymptomatic disease[5] and the increase in disability is re-

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lated to the accumulation of hypointense lesion load on T1-weighted images.[6,7] Although clinical endpoints remain the definitive measure of treatment efficacy, an effective therapy should also have a beneficial effect on an objective marker of disease activity such as MR imaging.

Three treatments have been proven to reduce the relapse rate and, possibly, have an effect on the natural course of relapsing-remitting multiple sclerosis (RRMS): interferon beta 1b,[8] Copolymer-1 (Cop1),[9] and interferon beta 1a.[10] Although the effects of the interferons on the pathologic process of the disease are strongly supported by MR imaging data—which show a decrease in the number of active brain lesions[10-13] and in the accumulation of the MR lesion load[11]—information on the effect of Cop1 on MR changes remains limited.[14]

In this study, the effect of Cop1 was evaluated in 10 patients with RRMS studied with serial gadolinium-diethylenetriamine penta-acetic acid (Gd)-enhanced MR imaging for a long period of time, comparing the monthly frequency of new Gd-enhanced lesions on T1-weighted images, the monthly enhanced area of the new enhancing lesions, and the rate of accumulation of lesion burden on T2-weighted scans during the baseline pretreatment period with the subsequent Cop1 treatment period.

Materials and methods. *Study design.* A baseline versus treatment design was used, with patients serving as their own controls,[1] similar to the design used by Stone et al.[13] to evaluate the effect of interferon beta 1b on contrast-enhanced MR imaging. Ten patients with clinically confirmed RRMS had monthly MR imaging for 9 to 27 months in the pretreatment period followed by 10 to 14 additional months with serial MR imaging during Cop1 treatment. T2-weighted scans and Gd-enhanced T1-weighted scans were obtained at each visit. Six of the 10 patients were followed for a long pretreatment period of 25 to 27 months and four patients were followed for 9 to 12 months before initiating treatment. All these patients were initially included in a study of MR imaging changes related to the natural course of the disease. At the end of the study, they were offered the opportunity to begin treatment with Cop1. The MR imaging-derived primary endpoint was the difference in the mean number of new Gd-enhancing lesions per month on T1-weighted images between the treatment and pretreatment periods. New enhancing lesions were defined as those that did not enhance in the preceding examination. Therefore, areas of persistent enhancement that enhanced on the preceding scan were not counted as new lesions.

Secondary study endpoints were the difference in the mean enhancing area/month of new Gd-enhancing lesions between the treatment and pretreatment periods; the difference in the proportion of months with at least one new Gd-enhancing lesion in the treatment versus the pretreatment period; or the change in rate of accumulation of le-

proved by the Ethics Committee of Genoa University and informed consent was obtained from each patient.

Patients and treatment. Entry criteria included a definite diagnosis of MS of the relapsing remitting type with at least two clinical relapses in the previous 2 years. The patients were not selected on the basis of the MR imaging activity. The patient group included four women and six men with a mean age of 36.6 ± 9.9 years and a mean disease duration of 12 ± 7 years. EDSS at baseline was 3.8 ± 1.25 and ambulation index 2.3 ± 1.06. EDSS at the end of pretreatment period was 4.1 ± 1.17. During the treatment, the patients received daily subcutaneous injections of 20 mg Cop1 (Copaxone).

MR protocol. The same 0.5-T imager (Esatom MR 5000; Esaote SpA, Genoa, Italy) was used during the entire trial period. Axial oblique images parallel to the bicommissural plane, with a slice thickness of 5-mm and 1-mm gap interslice, were acquired (field of view was 26.1 × 19.5 cm and matrix 192 × 256); spin-echo (SE) slightly T2-weighted images (TR/TE = 2000/30 ms, 1 excitation) were obtained and followed by SE T1-weighted images (TR/TE = 660/20 ms, 2 excitations) 5 minutes after intravenous administration of 0.15 mmol/Kg Gd (Magnevist Schering; Berlin, Germany). All images were photographed by a laser imager and stored on a magnetic tape. The guidelines stated by Miller et al.[15] were carefully observed.

Image analysis. MR images were segmented, patient by patient, using a semiautomated "growing region" software package by two radiologists (F.S., R.C.P.) masked to the scan date. The first radiologist segmented the Gd-T1-weighted images, counting the number of enhancing areas and determining the area of enhancement; the second radiologist examined the T2-weighted scans, obtaining the lesion load. The procedure of analysis was as follows: a T2-weighted or a Gd-T1-weighted image was randomly presented on the screen to the user, who did not know if the image belonged to the pretreatment or treatment period. The evaluation was therefore performed in a manner masked to the date of the scan. If one or more lesions were present, the user chose a top and bottom line and the median longitudinal axis of the cranial image. If this longitudinal axis was not perfectly vertical, the image was rotated moving the axis in vertical position before starting the segmentation. Examining image by image, the radiologist could identify and count each enhancing lesion by "clicking" a point inside the lesion with the mouse. The site of the lesion was defined by the software using two Cartesian coordinates. Lesion area of enhancement on T1- or lesion area on T2-weighted images was determined using a segmentation method based on a growing region, beginning from the seed identified by the operator clicking a point inside the lesion. The region then grows, including pixels spatially connected with signal levels between two thresholds that were calculated from the analysis of the signal level histograms of the lesion region of interest. The operator can change the thresholds to obtain the best covering of the lesion. This method was verified on a subset of the data obtained in this trial: 22 Gd-enhancing lesions on T1- and 42 lesions on T2-weighted images were selected and randomly presented to three radiologists who repeated

enhancing T1- and 40 lesions on T2-weighted images with both the growing region and standard manual contouring methods. All these data were evaluated with two-way analysis of variance ("fixed effect" model). The intraobserver variability was 3.8 pixels on T1-weighted images (3.7% of the total variability) and 5.9 pixels on T2-weighted images (2.1% of the total variability). The interrater variability was significant ($p = 0.02$) but appraised about 1 pixel for T1-weighted images, and was not significant for T2-weighted images. Data analysis showed that the growing region segmentation was affected by a reduced variance both for T1- and T2-weighted images ($p < 0.01$).[16] Therefore, the segmentation method used in this study was reproducible and less user-dependent than the standard manual contouring method.

Site, number of enhancing lesions, and area of enhancement of each lesion were recorded for each Gd-enhanced T1-weighted image; site and area of each lesion were recorded for each T2-weighted image. Number of enhancing lesions, enhancing area (mm^2) on Gd-enhanced T1-weighted images, and total lesion area (mm^2) on T2-weighted images were calculated per monthly scan.

To obtain the number of new Gd-enhancing lesions, a specific algorithm was elaborated.[17] To decide whether two lesions present on the same slice in two subsequent examinations are the same, the automated procedure uses an algorithm including Cartesian coordinates of the lesions, their area (schematized as circle), and a constant. The used algorithm is $(x_i - x_k)^2 + (y_i - y_k)^2 < (c(a_i^{1/2} + a_k^{1/2})^2)/\pi$, where x_i, y_i, and a_i are, respectively, the abscissa and the ordinate of the seed and the area of the lesion under analysis; x_k, y_k, and a_k are the same measurements calculated on the k-th lesion of the preceding MR scan; c is a constant to be calculated ($0 < c < 1$). When the inequality holds, the two lesions are considered as the same. The automatic determination of the new Gd-enhancing lesions was compared with the visual analysis of a subset of sequential scans; the c value was determined evaluating 27 enhancing lesions on Gd T1-weighted images. With $0.4 < c < 0.5$, all the lesions considered new in our study using the automatic method would have been considered new with a visual analysis.[17]

Percentage change from baseline in lesion area was calculated on T2-weighted images: for the six patients with the longest follow-up, the mean total lesion area was determined 2 years before treatment, 1 year before treatment, immediately before beginning treatment, and at the end of the treatment period. The same was calculated for all 10 patients, but without the −2 years measure.

Statistical analysis. The standard approach to evaluate the difference in the occurrence of lesions between pretreatment and treatment periods in studies with a baseline versus treatment design is, according to Nauta et al.[18] and Mc Farland et al.,[1] the Wilcoxon signed rank test, contrasting the mean number of lesions per month in the two periods in each patient. However, this approach has low statistical power as all observations in each patient are collapsed into a single figure, with a substantial loss of information. Therefore, to overcome this problem, we also analyzed the results in a secondary analysis as a series of single patient trials using the Mantel's extension of the weighted according to the number of new Gd-enhancing lesions. This approach is identical to that used in meta-analyses, as within-patient (each one considered as an independent trial) differences between observed and expected events are pooled into a summary test of significance, and is similar to that used by Moreau et al.[20] in a preliminary study evaluating the effect of the humanized monoclonal antibody CAMPATH-1H by monthly Gd-enhanced MR images. Using a similar approach, the proportion of scans with new Gd-enhancing lesions in the two periods was computed for each patient, to estimate the relative odds (odds ratio and 95% confidence limits) of having at least one new Gd-enhancing lesion at any month during the pretreatment period compared to the treatment period. A pooled estimate of the summary odds ratio among all patients was obtained by means of the Mantel-Haenszel procedure.[21] All analyses were conducted in patients using the entire pretreatment period and replicated focusing on the 12 months before initiating the treatment. As the results of the analyses closely resemble one another, only the former are presented.

Percentage changes in lesion area from baseline on T2-weighted images during the pretreatment and treatment periods were analyzed using the Friedman test. SPSS and SAS software were used for the statistical analyses.

Results. *New Gd-enhanced lesions.* During the pretreatment period, 477 areas of Gd enhancement were detected in all 10 patients, and 139 areas during treatment with Cop1. Of these areas, 397 during pretreatment and 115 during treatment were classified as new Gd-enhancing lesions.

Table 1 shows the mean rate of new Gd-enhancing lesions per scan before and during treatment with Cop1. Seven of the 10 patients had a 29% to 80% reduction in the number of lesions per scan. One patient had no lesions during the pretreatment period and 0.25 lesions per scan during treatment. One patient had no change (2/27 versus 1/13 lesions/scan) and one patient had an increase of 157%. The mean number of new Gd-enhanced lesions per scan in the pretreatment period was 2.20 compared to 0.92 during the Cop1 treatment period, indicating an average total reduction of 57% in lesions/scan ($p = 0.10$, Wilcoxon signed rank test).

To take advantage of the large number of scans performed and to obtain further information with a secondary analysis of a possible effect of Cop1, the number of new Gd-enhancing lesions observed in each scan were compared for each patient in the pretreatment and treatment periods. The results, pooled by means of the Mantel-Haenszel test, showed a significant reduction in the occurrence of new Gd-enhancing lesions during treatment (table 2; $\chi^2 = 8.77$; $df = 1$; $p = 0.003$). The reduction in the proportion of scans with new Gd-enhancing lesions during the period of treatment with Cop1 was also statistically significant. During the pretreatment period, 44% of scans showed at least one new Gd-enhancing lesion as compared to 29% of scans during the treatment period ($\chi^2 = 11.091$; $p = 0.001$); the odds ratio, computed as a weighted average of the patient specific odds ratio, was 0.40 (95% CI = 0.23 to 0.68).

Area of Gd-enhanced lesions. The mean enhancing

Table 1 *Mean rate of new gadolinium (Gd)-enhancing lesions during the pretreatment and treatment period*

	New Gd-enhancing lesions						
	Full pretreatment period			Treatment period			
Patient	Lesions	Months	Rate	Lesions	Months	Rate	% Difference
1	11	26	0.42	3	10	0.30	−29.09
2	16	25	0.64	2	13	0.15	−75.96
3	9	10	0.90	2	13	0.15	−82.91
4	2	27	0.07	1	13	0.08	+3.85
5	18	27	0.67	2	13	0.15	−76.92
6	98	10	9.80	56	13	4.31	−56.04
7	0	9	0.00	3	12	0.25	—
8	181	27	6.70	25	13	1.92	−71.31
9	55	25	2.20	6	14	0.43	−80.52
10	7	12	0.58	15	10	1.50	+157.14
Mean			2.20			0.92	−57.00
95% CI*			(0.07 ÷ 6.70)			(0.15 ÷ 1.92)	(−80.52 ÷ +3.85)
Median			0.66			0.28	−63.68

* Rank-based confidence intervals for the median.
$p = 0.1$ (Wilcoxon signed rank test).

quence, the decline in mean total area of Gd-enhanced lesions/month paralleled to the decrease in the number of enhancing lesions. The mean total area of new Gd-enhancing lesions/month during the pretreatment period was 43 ± 22 mm^2 compared to 22 ± 11 mm^2 during the Cop1 period ($p = 0.09$, Wilcoxon signed rank test). Examples of the number and area of new Gd-enhancing lesions on monthly MR images of four patients with the most active scans in the pretreatment period are shown in the figure.

Lesion load on T2-weighted images. The mean total lesion load on T2-weighted images was determined at different times: in the six patients with a longer pretreatment follow-up, there was an increase of lesion load of 24% between −2 years and −1 year and 8% between −1 year and treatment initiation; and a decrease of 4% between the beginning and end of treatment (Friedman $\chi^2 = 7.0$, $df = 2$, $p = 0.05$). For all 10 patients, there was an increase of 14% in the mean total lesion load from −1 year to treatment initiation, and a very small increase (+2%) from the beginning to the end of treatment ($p = 0.14$, Wilcoxon signed rank test).

Clinical data. All patients were examined every 3 months and within 3 days from a clinical relapse during both the pretreatment and treatment periods. During the pretreatment period, 42 confirmed relapses occurred com-

Table 2 *Number of scans with gadolinium (Gd)-enhancing lesions*

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7		Patient 8		Patient 9		Patient 10	
Number lesions	Pre-treat	Treat	Pre-treat	Treat	Pre-treat	Treat	Pre-treat	Treat	Pre-treat	Treat	Pre-treat	Treat	Pre-treat	Treat	Pre-treat	Treat	Pre-treat	Treat	Pre-treat	Treat
0	18	7	17	11	6	12	25	12	17	11	0	3	9	9	2	7	10	10	7	6
1	7	3	5	2	2	0	2	1	5	2	1	1	0	1	6	1	5	2	4	1
2	0	0	1	0	0	1	0	0	3	0	0	3	0	0	5	1	2	2	0	0
3	0	0	1	0	1	0	0	0	1	0	1	1	0	0	3	0	0	0	1	1
4	1	0	0	0	1	0	0	0	1	0	1	2	0	0	1	0	4	0	0	0
5	0	0	0	0	0	0	0	0	0	0	2	0	0	0	1	2	1	0	0	1
6	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	2	1	0	0	1
7	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
10+	0	0	0	0	0	0	0	0	0	0	4	2	0	0	6	0	1	0	0	0

pared to three relapses during the Cop1 treatment period. The yearly relapse rate was 2.5 during the pretreatment period and 0.3 during the treatment period. Corticosteroid therapy was given to treat 27 relapses during the pretreatment period and three relapses occurring during Cop1 treatment. The usual steroid therapy was intravenous methylprednisolone (1 g/day for 3 days; 0.5 g/day for 3 days; 0.25 g/day for 3 days). Occasionally, dexamethasone (8 mg intramuscularly for 2 weeks) or ACTH (50 U intramuscularly for 2 weeks) were also used. Considering the possible effect of steroid therapy on Gd enhancement, we repeated statistical analysis of the number of new Gd-enhancing lesions excluding the first month after each steroid treatment. The results were comparable to those obtained in the previous analysis (data not shown). The mean EDSS score was 3.8 at pretreatment baseline and 4.1 at the end of the pretreatment period. The mean EDSS score did not change at the final visit following 1 year of therapy.

Treatment with Cop1 was safe and well tolerated and adverse events were similar to those reported in previous trials of Cop1,[9] consisting of mild erythema and induration at the injection site and transient self-limited postinjection reaction, observed in three cases. This reaction occurred once in two patients and twice in the third, resolving spontaneously after a few minutes without sequelae.

Discussion. In this study, we examined the effect of Cop1 on MR changes in 10 patients with RRMS. Six patients had a very long pretreatment period of 25 to 27 months, four patients had a shorter pretreatment period of 9 to 12 months. All patients were subsequently treated with Cop1 for 10 to 14 months. Monthly Gd-enhanced MR imaging was performed both before and during treatment. The mean number of new Gd-enhancing lesions per month on T1-weighted images, the mean enhancing area/month of new Gd-enhancing lesions, the proportion of months with at least one new Gd-enhancing lesion, and the change in the accumulation of lesion load measured on T2-weighted images were determined in the periods before and during Cop1 treatment. A 57% decrease in the frequency of new Gd-enhancing lesions was obtained during treatment with Cop1 (mean, 0.92 per month; range, 0.08 to 4.31) as compared to the pretreatment period (mean, 2.20 per month; range, 0 to 9.80). Analysis of individual patients showed a reduction in 7 of 10 patients, two being inactive in both periods and one showing an increase in lesion frequency. When the p value for statistical significance was determined by means of the Wilcoxon signed rank test (the standard test for single crossover studies based on a baseline versus treatment design),[1,13,18] the difference of 57% between the number of new Gd enhancing lesions/month before and during treatment did not reach statistical significance ($p = 0.1$). However, the decrease in the occurrence of new Gd-enhancing lesions during the pretreatment period as compared to the treatment period achieved statistical significance ($p = 0.003$) were compared within each patient, and the results pooled over 10 patients, by means of Mantel's extension of the Mantel-Haenszel test.[19] The assumptions required for the use of this approach and its implications must be briefly discussed, along with the limitations of the study design.

The baseline versus treatment design, although widely used in trials in multiple sclerosis, has several drawbacks. Not only does it lack a randomized control group, but it cannot be accepted as a true crossover design; in fact, the treatment period always follows the "no treatment" period, and the sequence is not randomly determined for each patient. Patients may be more likely to be enrolled into a study in periods of increased disease activity: as a consequence, due to the spontaneous fluctuations of this activity, a reduction can be expected to occur independent of any treatment. This phenomenon, which can be defined as a form of regression to the mean, introduces a bias into this study (and in any study with the same design) that cannot be removed by any statistical technique. We tried to assess its size focusing on the six patients with longer pretreatment periods. This period was divided into early (initial 12 months) and late (12 months pretreatment) pretreatment periods. A clear decrease in the occurrence of new Gd-enhancing lesions was seen from the early to the late pretreatment period, confirming the presence of a substantial regression to the mean. However, the difference between the late pretreatment period and treatment period was still statistically significant using Mantel's extension of the Mantel-Haenszel test[19] (data not shown), supporting the hypothesis that Cop1 treatment was associated with a true reduction in the occurrence of new lesions.

The second point concerns the test used to assess statistical significance. The Wilcoxon test, suggested by McFarland et al.[1] and Nauta et al.[18] and widely used, has low statistical power in a setting like the current one, in which we have a small number of patients (10) but a high number of scans (observations) per patient (21 to 41 scans). The Wilcoxon test does not take into account the number of observations used to compute the mean number of lesions per observation. Therefore, a secondary analysis was performed to obtain further information on the possible effect of Cop1 on MR changes, following the approach used in another baseline versus treatment design[20] in which the results were treated as a series of single patient trials. The results were pooled over 10 patients using the same technique used in meta-analyses to pool data from several clinical trials. The Mantel extension of the Mantel-Haenszel test, which was used for assessing statistical significance in this study, requires the assumption that the number of new lesions at each observation is independent from the number at the preceding observation. This assumption is tenable, as visual inspection of our MR

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