Copaxone's effect on MRI-monitored disease in relapsing MS is reproducible and sustained

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Abstract—All but 6% of the subjects with relapsing remitting MS who were randomly assigned to receive glatiramer acetate or placebo for the 9-month controlled phase of the European/Canadian MRI trial entered an open-label extension with quarterly clinical and MRI evaluations for another 9 months. There was a 54% reduction in the mean number of enhanced lesions for those converted from placebo to glatiramer acetate and an additional 24.6% reduction for those always on glatiramer acetate. Over the entire study the accumulated T2 disease burden was 34.2% less for those always on glatiramer acetate.

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The initial placebo-controlled phase of this randomized two-phase trial showed that glatiramer acetate reduced MRI-measured disease activity and clinical attack rates,[1] by a magnitude similar to that found in prior studies.[2,3] The second study phase was preplanned to determine whether these effects were reproducible and sustained.

Methods. Eligibility required one or more relapses in the 2 years prior to trial entry and at least one enhancing lesion on a screening MRI.[1] All but one of 112 patients treated with glatiramer acetate and all 113 patients receiving placebo who completed the double-blind phase agreed to open-label therapy. Study drug exposure was 18 months with scheduled visits at screening and baseline, nine monthly visits during the double-blind phase, and three quarterly visits during the open-label phase. All patients were evaluated within 7 days of a relapse. MRI metrics were determined without knowledge of treatment assignment.[1]

Efficacy analyses were intent-to-treat for the cohort that entered open-label treatment with a last-observation-carried-forward imputation. The results reported here for the 9-month controlled phase differ from those previously reported in that the number of patients is limited to those who entered the open-label extension, and the MRI metrics are provided at quarterly intervals to balance imaging frequency during the two study phases. Patients originally assigned to receive glatiramer acetate were compared with those originally on placebo using descriptive statistics as well as multivariate analyses with derived MRI and relapse measures as dependent variables, and demographic and baseline MS and MRI parameters as explanatory variables. Due to the skewed distribution of MRI measures, analyses were repeated using original as well as rank transformed variables. Analyses were performed for the placebo-controlled and open-label phases and the entire study.

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Results. The baseline demographics and MS disease characteristics of the 224 patients who entered the open-label trial were similar to those of the entire randomized cohort.[1] Some disease characteristics differed statistically at crossover due to treatment. Two original glatiramer acetate–treated and seven patients receiving placebo did not complete the extension. Several reasons accounted for subject loss during the two phases of the trial (11 adverse experiences, 5 withdrew consent, 2 refused further MRI, 1 pregnancy, 1 lost to follow-up, 3 other).

The primary outcome was the mean number of enhanced lesions observed per subject at monthly intervals summed over the 9-month placebo-controlled phase.[1] An effect similar to that reported for all randomized patients was found for the subcohort of patients who entered the open-label trial using only quarterly scan data (figure ; p = 0.001). The number of enhancing lesions over the 9-month open-label extension was comparable ($p = 0.82$). The magnitude of reduction in total enhancements over the first 9 months of active treatment for those beginning glatiramer acetate during the open-label phase (54%) was marginally greater than for those originally randomly allocated to receive glatiramer acetate (46.5%). Over the entire study

*See the Appendix for a list of the investigators, roles, and industry affiliations of the members of The European/Canadian Glatiramer Acetate Study Group.

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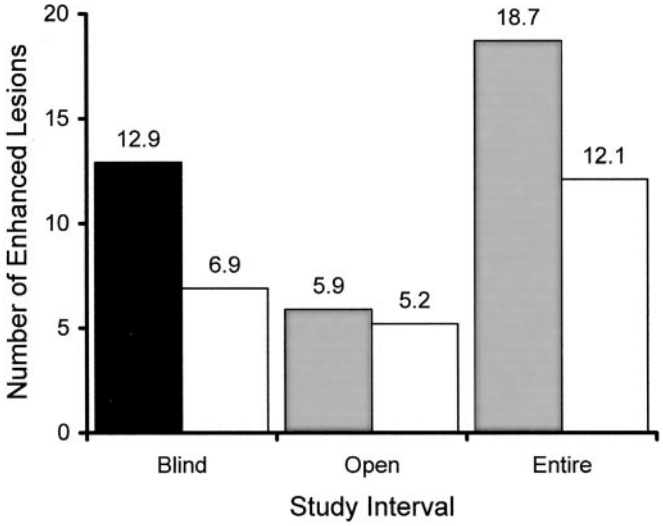

Figure. Number of enhanced lesions on T1-weighted post-gadolinium injection images by study phase. The original placebo randomized group is displayed as a black bar during the first 9 months and as a gray bar during the second 9 months and entire 18-month interval to differentiate when they were exposed to active treatment with glatiramer acetate (GA). Those initially randomly assigned to receive GA are always shown as white bars. The cumulative mean number of enhancements observed on the quarterly scans during the placebo-controlled phase of the study are displayed for the evaluable cohort: (blind; placebo 12.9 ± 20.3 SD [median, 6.0; range, 0 to 147], GA 6.9 ± 11.7 [3.0; 0 to 89]), open-label phase of the trial (open; 5.9 ± 11.1 [2.0; 0 to 87] for those starting GA after 9 months of placebo treatment, 5.2 ± 11.9 [1.0; 0 to 81] for those always on GA) and over the entire 18-month study (entire; placebo initially 18.7 ± 28.9 [9.0; 0 to 234], always GA 12.1 ± 20.3 [5.0; 0 to 126]).

those treated continuously with glatiramer acetate showed 35% fewer enhancements ($p = 0.03$). Thus, the 9-month delay in initiating therapy resulted in six "preventable" enhancing lesions per patient. When analyzed following rank transformation, the results favored those originally randomly assigned to receive glatiramer acetate over the placebo-controlled period ($p = 0.0001$), entire 18-month observation ($p = 0.0001$), and during the 9-month open-label phase ($p < 0.002$).

The number of T1 gadolinium-enhancing lesions on quarterly images during the double-blind phase was always lower in the glatiramer acetate group (see table E1 on the *Neurology* Web site), with a trend seen at Month 3 that strengthened by Months 6 and 9 (both $p < 0.001$). During the open-label phase, the proportion of enhanced lesion-free patients increased to 63% at Month 18 for those always on glatiramer acetate. Patients who crossed over exhibited a response very similar to that found for the glatiramer acetate group during the double-blind phase; within 3 months of their switch to glatiramer acetate the proportion of enhanced lesion-free subjects increased from 31 to 45%, and it had risen to 60% by the end of the trial (see table E1). The median cumulative change from baseline enhanced lesion volume also proved similar once glatiramer acetate treatment was initiated (see table E1).

The T2 lesion volume increased during the double-blind phase in both groups (see table E1), and differences in median percent change from baseline between the groups persisted over the entire 18-month study ($p < 0.02$). Whereas the T2 disease burden showed little change during the open-label phase for either group, those switched from placebo to glatiramer acetate maintained a greater increase from baseline (3.8 ± 12.3 mL [median 2.6, range −100 to 49.7]) than those always treated with glatiramer acetate (2.4 ± 4.5 mL [1.9, −18.2 to 15.8]).

An increase in T1 hypointense volume was observed in both treatment groups over both trial phases (see table E1). The increase was less over the double-blind phase for those patients on glatiramer acetate than for those on placebo ($p < 0.05$ for drug-by-time interaction), with the largest differences evident at Month 9. Over the entire 18-month study, the 9-month delay in the initiation of treatment with glatiramer acetate was associated with a 2.2-fold increase in the accumulated hypointense lesion volume (median change from entry of 1.06 mL and 0.49 mL), a nonsignificant trend. The effect of glatiramer acetate on the resolution of serially studied newly formed hypointense lesions is addressed elsewhere.[4]

By the end of the double-blind phase, a 29% difference in the baseline-adjusted number of relapses favored glatiramer acetate ($p < 0.05$). All patients had a further reduction in relapse rate during the open-label phase. Total relapses by study quarter are shown in table E1. No major changes from baseline EDSS scores were noted at any time.

One or more adverse events were reported by 105 patients always on glatiramer acetate and by 91 patients exposed to glatiramer acetate only for the last 9 months. The vast majority of these events were mild to moderate, with only 10% considered severe. Most commonly reported were erythema and pain at injection sites and components of the immediate postinjection reaction. Most subjects reported adverse events that lasted >1 day and nearly all adverse events were deemed treatment related. Seven patients in the evaluable cohort withdrew due to adverse experiences; four of these related to injection site reactions.

Twelve patients had 14 serious adverse events while on glatiramer acetate; accidental injury accounted for four. Four serious events were considered severe. Only two serious events were considered related to some extent to study medication. Drug was temporarily interrupted for palpitations in one subject but was restarted without recurrence. The other serious event was moderate pain, which resolved with continued treatment. None discontinued therapy due to a serious adverse event, although in four cases treatment was temporarily interrupted. All patients recovered.

Discussion. This study incorporated several trial designs in a study population enriched for MRI activity. The first phase used a standard parallel-group trial design. The second study phase was designed to determine whether MRI-related treatment effects were reproduced on initiation of glatiramer acetate (a crossover design) and to establish whether the effects were sustained (open-label extension). The treatment effects seen during the first study phase were reproduced when patients initially randomly assigned to receive placebo were started on glatiramer acetate and were maintained for those who

continued on glatiramer acetate. The reduction in the number of enhancements on quarterly scans within 9 months of starting glatiramer acetate was similar for both groups at 52.5 and 62.8%. The trial design may also be viewed as a randomized delayed start of therapy. Early initiation of therapy resulted in 6.6 fewer enhanced lesions on the quarterly scans, and 5.3 fewer new T2 lesions for patients always on glatiramer acetate than in those randomly assigned to a delay.

Appendix

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G. Comi, M. Filippi, J.S. Wolinsky, D. Ladkani*, S. Kadosh*, and G. Shifroni* were involved in the data analyses and interpretation and in writing the manuscript. The original version of the paper was distributed for comments and approval to the study trialists through the principal investigators at each participating site before being finalized. Teva Pharmaceutical, Ltd. supported this work; * = employees of Teva Pharmaceutical, Ltd.

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Table (E)T-1: Clinical Measure Changes on Study

		Month on Study						
		0	**3**	**6**	**9**	**12**	**15**	**18**
Enhancement Number - Total								
	GA [1]	4.0 ± 4.4 [3] 2.0 (0, 19) [4]	3.2 ± 5.9 1.0 (0, 45)	1.8 ± 3.6 1.0 (0, 28)	1.9 ± 3.4 1.0 (0, 18)	2.1 ± 5.0 0 (0, 31)	2.0 ± 7.9 0 (0, 78)	1.2 ± 3.1 0 (0, 20)
	PBO[2]	4.5 ± 7.2 2.0 (0, 49)	5.2 ± 10.2 2.0 (0, 61)	3.4 ± 5.3 2.0 (0, 29)	4.3 ± 8.7 1.0 (0, 57)	2.6 ± 5.1 1.0 (0, 38)	1.6 ± 3.3 0 (0, 21)	1.6 ± 3.8 0 (0, 28)
Enhancement Free (%)								
	GA	18.9	35.1	46.8	47.7	52.3	61.3	63.1
	PBO	17.7	31.9	32.7	31.0	45.1	50.4	60.2
Enhanced Tissue Volume in ml								
	GA	0.53 ± 0.67 0.31 (0, 2.8)	0.44 ± 0.84 0.12 (0, 6.2)	0.27 ± 0.61 0.05 (0, 4.5)	0.27 ± 0.54 0.06 (0, 3.1)	0.28 ± 0.71 0 (0, 5.2)	0.23 ± 0.73 0 (0, 6.1)	0.14 ± 0.36 0 (0, 2.8)
	PBO	0.74 ± 2.26 0.24 (0, 23)	0.70 ± 1.33 0.16 (0, 6.7)	0.46 ± 0.70 0.17 (0, 3.3)	0.63 ± 1.50 0.14 (0, 13)	0.37 ± 0.77 0.06 (0, 5.6)	0.24 ± 0.49 0 (0, 2.5)	0.23 ± 0.70 0 (0, 5.7)
T2 Lesion Volume in ml								
	GA	18.7 ± 15.3 14.1 (2, 89)			21.9 ± 17.3 17.5 (2.1, 93)			21.2 ± 16.0 18.1 (2.1, 91)
	PBO	20.9 ± 19.0 16.4 (2, 143)			25.7 ± 19.7 20.7 (1.7, 96)			24.7 ± 19.2 24.7 (0.1, 108)
New T2 Lesions								
	GA					1.6 ± 2.7 1.0 (0, 15)	1.4 ± 4.4 0 (0, 43)	1.1 ± 2.0 0 (0, 14)
	PBO					2.3 ± 3.2 1.0 (0, 18)	1.4 ± 2.6 1.0 (0, 18)	1.1 ± 2.1 0 (0, 12)

Baseline T1 Hypointense Lesion Volume and Change from Baseline in ml								
	GA	3.3 ± 3.9 1.8 (0, 24)	0.42 ± 1.47 0.1 (-6, 6)	0.56 ± 1.42 0.2 (-5, 6)	0.80 ± 1.96 0.3 (-6, 7)	0.74 ± 1.86 0.3 (-6.5, 8)	0.76 ± 1.94 0.3 (-6.5, 9)	1.22 ± 2.35 0.5 (-6.5, 12)
	PBO	4.1 ± 5.0 2.9 (0, 32)	0.13 ± 1.92 0.1 (-17, 5)	0.41 ± 2.43 0.1 (-18, 10)	1.39 ± 2.71 0.5 (-3, 16)	1.13 ± 2.75 0.5 (-14, 14)	1.11 ± 2.59 0.6 (-11, 13)	1.57 ± 3.31 1.1 (-10, 17)
Relapses by Quarter								
	GA		29	24	8	12	7	12
	PBO		31	20	29	16	11	12
Baseline and Change from Baseline Extended Disability Status Score (EDSS)								
	GA	2.3 ± 1.1 2.0 (0, 5)			-0.01 ± 0.79 0 (-2.5, 3.0)			-0.07 ± 0.92 0 (-3.5, 3.0)
	PBO	2.4 ± 1.2 2.0 (0, 5)			0.04 ± 0.86 0 (-2.0, 3.0)			0.03 ± 0.92 0 (-2.0, 4.0)

[1]GA = glatiramer acetate for 18 months

[2]PBO = placebo for 9 months, then GA for 9 months

[3] unadjusted mean ± standard deviation

[4] median, (minimum value, maximum value)

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