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Short-Term Correlations between Clinical and MR Imaging Findings in Relapsing-Remitting Multiple Sclerosis

Marco Rovaris, Giancarlo Comi, David Ladkani, Jerry S. Wolinsky, Massimo Filippi, and the European/Canadian Glatiramer Acetate Study Group

BACKGROUND AND PURPOSE: Despite extensive use of MR imaging to provide markers of multiple sclerosis (MS) activity and accumulated disease burden, the magnitude of the relationship between clinical and MR findings is still debated. Using data from the European/Canadian glatiramer acetate (GA) trial, we investigated short-term correlations between clinical and MR measures of disease activity in patients with relapsing-remitting MS (RRMS).

METHODS: In a 9-month, double-blinded, placebo-controlled study, 239 patients with RRMS were randomly assigned to receive 20 mg GA (n = 119) or placebo (n = 120). Clinical assessment included monthly neurologic examinations with Expanded Disability Status Scale scoring and visits for symptoms suggestive of relapse. Dual-echo T2-weighted and pre- and postcontrast T1-weighted brain MR images were obtained at baseline and monthly during follow-up. Contrast-enhancing and new T2-hyperintense lesions were counted, and total T2-hyperintense and T1-hypointense lesion volumes were measured.

RESULTS: Significant univariate correlations were found between the number of relapses during the study period and the number of enhancing lesions at baseline (r = 0.25) and during follow-up (r = 0.30) in the study population as a whole. Multivariable analysis showed that two independent factors were more strongly correlated with relapse frequency: the number of relapses during the 2 years before entry and the number of on-trial enhancing lesions, in the whole study population and in the placebo group.

CONCLUSION: In RRMS, MR imaging measures of inflammatory activity are modestly but significantly correlated with the occurrence of clinical attacks over the short term. Clinical and MR imaging assessment can provide complementary outcome measures for RRMS trials.

In multiple sclerosis (MS), MR imaging of the brain can provide numerous markers of disease activity and evolution (1). These include the number of contrastenhancing lesions and new T2-hyperintense lesions, as counted on serial images, and the overall burden of T2-hyperintense or T1-hypointense lesions (1, 2). MR-derived measures have clear advantages over clinical assessment, including their more objective nature and their greater sensitivity to MS-related

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changes (2). However, it remains disappointing that, in patients with established MS, the results from several studies (3-13) consistently showed a limited correlation between MR measures of accumulated burden of disease and clinical disability. The relationship between MR-visible activity and the occurrence of relapses is also moderate at best (8–12). The exception may be MR metrics in patients with clinically isolated syndromes suggestive of MS (14, 15). In addition, although several immunomodulating and immunosuppressive treatments favorably modify several MR-derived outcomes in phase II and III trials of MS (16-20), the magnitude of this effect was always greater than that of the corresponding clinical measures of disease activity and progression (16-20). Nevertheless, because of its sensitivity, MR imaging will most probably remain a widely used paraclinical tool in future trials of new treatments for MS in which placebo arms will be unethical and comparisons with available therapies will require large patient samples for adequate study power (21). All of these data

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indicate that, to define the use of MR imaging as a surrogate marker of disease activity and evolution, the correlation between clinical and MR imaging findings in MS patients must be investigated more extensively.

We have recently conducted a parallel-group, randomized, double-blinded, placebo-controlled study (22) that showed the efficacy of glatiramer acetate (GA) (Copaxone; Teva Pharmaceutical Industries, Ltd, Israel) on clinical and MR imaging measures of relapsing-remitting MS (RRMS) activity. In this trial, the MR imaging acquisition and postprocessing protocol was designed by following international consensus guidelines (2) established to optimize the accuracy, reproducibility, and sensitivity of MR-derived measures for MS studies. In addition, the placebo group in this trial is one of the largest samples of patients with RRMS ever examined with monthly MR imaging during a period of more than 6 months. For these reasons, data from the European/Canadian GA trial offered the unique opportunity to readdress several issues related to clinical-MR imaging correlations in MS by using MR data accurately collected from a large patient sample. In the present study, the trial dataset was analyzed to investigate the relationship between MR imaging and clinical outcomes, as well as the correlation between different MR measures.

Methods

Participants

To participate in this study, subjects had to be aged 18–50 years (inclusive) and they had to have a diagnosis of clinically definite MS (23) for at least 1 year, a RRMS disease course (24), an Expanded Disability Status Scale (EDSS) score (25) of 0.0–5.0, at least one documented relapse in the preceding 2 years, and at least one contrast-enhancing lesion on their screening brain MR images. Subjects had to be clinically relapse-free and without steroid treatment in the 30 days before their inclusion into the study. Additional information about the inclusion and exclusion criteria is reported elsewhere (22). The ethics committees of all participating centers approved the study protocol, and each patient provided written informed consent before trial entry.

Study Design

The study was a double-blinded, placebo-controlled, randomized study of 9-month duration. For trial purposes, a month was defined as 4 weeks (28 days \pm 7). Treatment consisted of the daily administration of 20 mg GA or placebo by means of subcutaneous injection. All patients underwent physical and neurologic examination, including EDSS rating; laboratory studies; and brain MR imaging at screening, baseline, and every month. Additional neurologic assessments were performed for symptoms suggestive of a relapse. A relapse was defined as the appearance or reappearance of one or more new or previous neurologic symptoms. Patients were instructed to call their local center immediately if they perceived that they might be experiencing a relapse. A visit was arranged within 7 days of their notification. Neurologic deterioration had to last at least 48 hours and be preceded by a relatively stable or improving neurologic state in the prior 30 days. An event was counted as a relapse only when the symptoms were accompanied by objective changes in the neurologic examination corresponding to an increase of at least a half point on the EDSS or one grade in the score of 2 or more Functional Systems (FS), or two grades in 1 FS. Deterioration associated with fever or infection that can cause transient secondary impairment of neurologic function in patients with MS was not considered a relapse. Similarly, a change in bowel, bladder, or cognitive function alone was not accepted as a relapse. Relapses could be treated with 1.0 g of methylprednisolone intravenously administered on a daily basis for 3 consecutive days.

MR Imaging Acquisition and Analysis

Conventional spin-echo sequences (TR/TE, 2200-2800/20-50, 60-100) were used to obtain proton density- and T2weighted images. Two series of T1-weighted images (450-650/ 10-20) were obtained before and 5 minutes after the injection of 0.1 mmol/kg of gadolinium-based contrast material. Fortyfour 3-mm-thick contiguous axial sections positioned parallel to a line that joined the most inferoanterior and the inferoposterior parts of the corpus callosum were always acquired. At follow-up, patients were carefully repositioned according to published guidelines (26). The Neuroimaging Research Unit conducted the entire image analysis in Milan. After hyperintense lesions were identified on the dual-echo T2-weighted images and after contrast-enhancing and hypointense lesions were identified on the contrast-enhanced T1-weighted images, new contrast-enhancing and new T2-hyperintense lesions were counted on the follow-up images. Two experienced observers identified the lesions by consensus. Trained technicians then outlined the lesions by using a semi-automated segmentation technique based on local thresholding, with reference to the marked hardcopies. Total T2-hyperintense and T1-hypointense lesion volumes were calculated automatically, as previously described (22).

Statistical Analysis

The correlations between clinical and MR imaging findings in the entire study population and in each treatment group in isolation, as well as those between different MR imaging metrics, were assessed by using the Spearman rank correlation coefficient. The correlation between clinical and MR imaging activity was also investigated by using a multivariate analysis with the number of relapses during the study period as the dependent variable and the following explanatory variables: the number of relapses during the 2 years preceding study entry, the number of contrast-enhancing lesions at baseline, the total number of contrast-enhancing lesions during the study months, the total number of new T2-hyperintense lesions during the study months, the study site, and the drug effect. Similar models were used to evaluate this correlation in the GA and placebo groups separately (in the latter case, without drug effect among the explanatory variables). The numbers of contrast-enhancing lesions and new T2-hyperintense lesions were incorporated into the models after a rank transformation was performed. Clinical and MR imaging variables, which were consistently found to be not significant along the different models, were removed to obtain the final results.

For both clinical and MR imaging parameters, the last observation carried forward (LOCF) approach was used in case of missing data. The robustness of the results was always verified by analyzing the data as is; that is, with no imputation for missing data. The results of as-is analysis were always consistent with the LOCF results (data not shown).

Results

Of the 239 enrolled patients, 119 were randomly assigned to the GA group, and 120 were assigned to the placebo group. Baseline demographic, clinical, and MR imaging characteristics did not differ significantly between the two study arms (Table 1). Seven

 TABLE 1: Baseline clinical and MR imaging characteristics of the study subjects

Characteristic	Placebo Group (n = 120)	GA Group $(n = 119)$
Age (y)	34.0 ± 7.5	34.1 ± 7.4
Disease duration (y)	8.3 ± 5.5	7.9 ± 5.5
Prior 2-year relapse rate	2.5 ± 1.4	2.8 ± 1.8
EDSS score	2.4 ± 1.2	2.3 ± 1.1
No. of Gd-enhancing lesions	4.4 ± 7.1	4.2 ± 4.8
Volume of lesions (cm ³)		
Gd enhancing	0.7 ± 2.2	0.6 ± 0.7
Hyperintense on T2-weighted images	20.5 ± 18.8	20.0 ± 17.2
Hypointense on T1-weighted images	4.0 ± 4.9	3.4 ± 3.9

Note.—Data are the mean \pm SD.

patients dropped out in each arm. Additional information about the reasons for individual patient dropouts are reported elsewhere (22). GA treatment proved to be effective in reducing the frequency of enhancing and new T2 lesions and of increases in T2 lesion volume. A considerable treatment effect was also found in the frequency of clinical relapses. The statistical methods used in these analyses and additional information about the trial results are reported elsewhere (22).

The univariate correlations between clinical and MR-measured MS activity are presented in Table 2. The number of relapses reported during the 2 years preceding study initiation was weakly but significantly correlated with the number of relapses and the number of new T2 lesions counted during follow-up. The number of relapses during the study period was significantly correlated with both the number of enhancing lesions at baseline and the number of enhancing lesions at baseline and the study period. Strong correlations were observed between enhancing lesions at baseline and those counted during the study period and between the number of enhancing lesions and the number of enhancing lesions and the number of new T2 lesions.

In the patient sample as a whole, the number of enhancing lesions counted during the first trimester of the study was significantly correlated with the number of clinical relapses during the same period (all patients, r = 0.19, P = .004; placebo arm, r = 0.18, P < .05; GA arm, r = 0.19, P = .04). The same was

true in the subsequent 3 months (all patients, r = 0.15, P = .02; placebo arm, r = 0.25, P = .007; GA arm, r = 0.05, P = .59). The correlation of this MR-derived parameter with the occurrence of relapse in the last trimester of the trial period was not significant for the GA treated group when the two study arms were considered in isolation (all patients, r = 0.13, P < .05; placebo arm, r = 0.26, P = .004; GA arm: r = -0.12, P = .19).

That the frequency of enhancement and the occurrence of relapses were correlated was confirmed by the finding that patients who experienced at least one relapse during the study period had a higher mean number of contrast-enhancing lesions (ie, 42.3 lesions) than those who did not (ie, 19.7 lesions) (P <.001, Mann-Whitney test). For patients with and for those without relapse, the mean number of contrastenhancing lesions was 50.4 and 21.7 for patients in the placebo group (P = .003, Mann-Whitney test) and 33.1 and 17.8 for GA-treated patients (P = .02, Mann-Whitney test), respectively.

The multivariate regression model showed that the number of relapses during the study period was correlated with the number of relapses in the 2 years before randomization (P = .005) and with the drug effect (P < .02) but not with the study center. When the number of contrast-enhancing lesions at baseline was added as an additional explanatory variable in the model, it was found to be a significant predictor of the number of relapses during the study period (P <.001). Drug effect and number of relapses in the 2 years before randomization remained significant. When the total number of contrast-enhancing lesions seen during the study was added, this was also found to be a significant predictor of the number of relapses during the study period (P < .001), but the drug effect and the number of contrast-enhancing lesions at baseline became nonsignificant. When the number of new T2 lesions was added, it was not significant. Thus, the final multivariate model included the number of relapses in the 2 years before randomization and the total number of contrast-enhancing lesions during the study period as independent explanatory variables for the number of on-trial relapses.

Similar multivariate analyses were also performed

TABLE 2: Univariate correlations between clinical and MR imaging measures of MS disease activity

Variable 1*	Variable 2*	All Patients $(n = 239)$	Placebo Group ($n = 120$)	GA Group $(n = 119)$
Pre-study relapses	On-trial relapses	0.21 (.001)	0.19 (.04)	0.25 (.006)
Pre-study relapses	Baseline EL	0.10	0.09	0.11
Pre-study relapses	On-trial EL	0.15 (.02)	0.14	0.20 (.03)
Pre-study relapses	On-trial new T2 lesions	0.19 (.003)	0.15	0.27 (.003)
On-trial relapses	Baseline EL	0.25 (<.001)	0.30 (.001)	0.22 (.02)
On-trial relapses	On-trial EL	0.30 (<.001)	0.36 (<.001)	0.21 (.02)
On-trial relapses	On-trial new T2 lesions	0.32 (<.001)	0.34 (<.001)	0.25 (.006)
Baseline EL	On-trial EL	0.64 (<.001)	0.66 (<.001)	0.65 (<.001)
On-trial EL	On-trial new T2 lesions	0.88 (<.001)	0.90 (<.001)	0.84 (<.001)

Note.—Values are the Spearman rank correlation coefficients. Data in parentheses are P values $\leq .05$.

*Pre-study relapses indicate the number of relapses during the 2 years prior to the study period; baseline EL, the number of Gd-enhancing lesions on the images obtained at study entry; and on-trial EL, the total number of Gd-enhancing lesions during the 9 months of the study.

	EDSS Score, (n =	All Patients 239)	EDSS Score, F (n =	Placebo Group 120)	EDSS Scor (n =	e, GA Group = 119)
Measure	Baseline	Change	Baseline	Change	Baseline	Change
Baseline T2 LV	0.28 (<.001)	0.16 (.02)	0.27 (.003)	0.09	0.29 (.001)	0.24 (.008)
Baseline T1 LV	0.19 (.003)	0.18 (.006)	0.24 (.009)	0.12	0.12	0.23 (.01)
T2 DLV	0.13	0.17 (.007)	0.12	0.10	0.10	0.25 (.005)
T1 DLV	0.17 (.007)	0.18 (.006)	0.16	0.09	0.20 (.03)	0.31 (<.001)

TABLE 3: Univariate correlations between MR imaging measures of MS burden of disease and clinical disability

Note.—Values are the Spearman rank correlation coefficients. Data in parentheses are P values $\leq .05$. DLV indicates the difference in lesion volume between month 9 images and baseline images; EDSS change, the difference in the EDSS score between month 9 evaluations and baseline evaluations; and LV, lesion volume.

TABLE 7. Univariate correlations between with imaging measures of who activity and buruen of unseas

Variable 1*	Variable 2*	All Patients $(n = 239)$	Placebo Group (n = 120)	GA Group $(n = 119)$
Baseline T2 LV	On-trial EL	0.51 (<.001)	0.55 (<.001)	0.47 (<.001)
Baseline T2 LV	On-trial new T2 lesions	0.32 (<.001)	0.40 (<.001)	0.24 (.009)
Baseline T2 LV	T2 DLV	0.37 (<.001)	0.44 (<.001)	0.30 (.001)
Baseline T2 LV	T1 DLV	0.50 (<.001)	0.48 (<.001)	0.53 (<.0001)
Baseline T1 LV	On-trial EL	0.36 (<.001)	0.41 (<.001)	0.29 (.001)
Baseline T1 LV	On-trial new T2 lesions	0.19 (.003)	0.28 (.002)	0.10
Baseline T1 LV	T1 DLV	0.29 (<.001)	0.33 (<.001)	0.24 (.009)
Baseline T1 LV	T2 DLV	0.17 (.007)	0.22 (0.02)	0.13

Note.—Values are the Spearman rank correlation coefficients. Data in parentheses are P values $\leq .05$.

*DLV indicates the difference in lesion volume between month 9 images and baseline images; LV, lesion volume; on-trial EL, the total number of Gd-enhancing lesions during the 9 months of the study.

for the GA and the placebo groups in isolation. For the GA group, the total number of contrast-enhancing lesions at baseline was predictive of the number of relapses during the study period (P = .007), whereas the number of relapses in the 2 years before randomization became nonsignificant. For the placebo group, both the number of relapses in the 2 years before randomization and the total number of enhancing lesions during the study period were significant predictors of the number of relapses observed during the trial (P = .006 and P = .003, respectively).

Table 3 shows the univariate correlations between MR imaging measures of lesion burden and the EDSS score. In the entire patient sample, both T2hyperintense and T1-hypointense lesion volumes at baseline were significantly correlated with the baseline EDSS score. Changes in MR lesion volumes and EDSS scores were significantly correlated in the entire patient sample and in the GA group. No significant correlations were found between the total number of new T2 lesions accumulated over 9 months and the patients' baseline values or changes in the EDSS score (data not shown).

Table 4 shows the univariate correlations between MR imaging measures of MS activity and the accumulated burden of disease. Both T2 and T1 lesion volumes at baseline were significant predictors of the amount of MR imaging activity during the study period. T2 and T1 lesion volumes at baseline were also significantly correlated with the corresponding changes observed during the subsequent 9 months. The median ratio between T1-hypointense and T2hyperintense lesion volumes at baseline was 15.2% (range, 0.0-49.2%) in the study population as a whole; this value did not differ significantly between placebo patients and GA patients (data not shown). No significant univariate correlations were found between baseline T1/T2 ratio and the on-trial number of relapses and number contrast-enhancing lesions. This parameter was not included in any multivariable model in either the study population as a whole or in any of the two treatment arms in isolation (data not shown).

Steroid courses were administered to 33.6% and 39.2% of the GA patients and placebo patients, respectively. A total of 84 steroid-treated relapses were noted among the placebo group, and 54 steroid-treated relapses occurred among those receiving GA. The results of the correlative analysis did not change after we corrected for the steroid treatments.

Discussion

Although brain MR imaging is widely used to provide markers of MS disease activity and evolution, the correlation between clinical and MR findings has been found to be moderate, at best (3–13). However, in some previous studies of the clinical–MR imaging relationship, the samples of MS patients were relatively small (9, 10, 12) or clinically heterogeneous (3–6, 8, 13). Therefore, the actual value of MR imaging in predicting MS clinical activity and progression is still a matter of debate.

In this study, we analyzed the data from a doubleblinded, placebo-controlled trial to assess the efficacy of GA treatment in RRMS (22). Our aim was to

investigate the correlations between clinical and MR imaging patterns of disease evolution over a short period. In comparison with previous investigations, this study had several advantages, including its large sample size, the high degree of ongoing disease activity (patients were selected for the presence of contrast enhancement on a screening image) (22), the duration of MR follow-up with monthly images (longer than that of any previous study), and the uniformity of the MR imaging protocol (which was designed in accordance with international guidelines for the use of MR imaging in trials of MS) (2). Because of the high correlation between total numbers and volumes of enhancing lesions in RRMS (r = 0.9) (27), we decided not to include the latter parameter among the MR imaging measures of MS activity to reduce the risk of type I errors.

We found that, in RRMS, a moderate correlation exists between MR imaging-measured disease activity and clinical relapses, in agreement with the results of previous studies (8, 9, 12). However, the extent of MR imaging activity at a given time (ie, the number of contrast-enhancing lesions on a single baseline image) was only weakly predictive of the occurrence of relapses in the subsequent 9 months. In the metaanalysis by Kappos et al (8), who did not select patients for the presence of baseline MR imaging activity, the impact of initial contrast enhancement on the subsequent relapse rate was even weaker; this result again highlighted the great interpatient variability and the low predictability of the course of MS. In addition, when longitudinal data were analyzed on a trimester-by-trimester basis, the predictive value of MR imaging activity for the subsequent occurrence of relapses in patients receiving placebo was found to be modest (r < 0.3). This means that, in a group of RRMS patients selected for having baseline MR imaging activity, the frequency of enhancement on three consecutive monthly images accounts for less than 10% of the variability in relapse occurrence 4-6months after the last imaging examination. As a consequence, our findings suggest that caution must be exercised when one considers MR-derived measures as potential predictors of subsequent MS evolution, particularly in cases of individual patient monitoring. However, a correlation between increased MR imaging activity and later clinical impairment cannot be definitively ruled out with the present results, given the relatively short duration of the study. The results of previous studies (8, 10) also seem to suggest that higher initial activity on contrast-enhanced MR images might be correlated with a more rapid progression of MS disability after long-term follow up.

In view of the modest strength of the short-term correlations between the frequency of enhancing lesions and that of clinical relapses, the use of contrastenhanced MR imaging seems not to be recommended to provide primary efficacy measures in phase III RRMS trials, which usually last for 1–2 years. This is also consistent with data from recent studies of patients with secondary progressive MS (10, 11, 13). The role of MR-derived measures as primary outcomes should, therefore, be limited to exploratory and phase II MS trials, because their usefulness in detecting inflammatory disease activity is not fully translated into a predictive value for clinical MS evolution. These findings also indicate that the application and development of quantitative MR techniques with increased sensitivity and specificity for the most destructive aspects of the disease might help us to overcome such a clinical–MR imaging paradox, especially when used together with the functional MR imaging assessment of the mechanisms of cortical adaptive reorganization (which may limit the clinical consequences of MS injury) (28).

As expected, the mutual correlations between MRderived measures of MS activity (counts of active lesions) and the accumulated burden of disease (total T2-hyperintense and T1-hypointense lesion volumes) were almost all significant and of moderate strength. Our results indicate that selecting patients with RRMS for the presence of contrast enhancement on a screening image increases the harvest of enhancing lesions during the subsequent period, as shown in previous studies (8, 9). We found a strong, albeit incomplete, correlation between contrast-enhancing lesions and new T2 lesions during follow-up (r = 0.90in the group receiving placebo). This finding suggests that, when serial monthly images are available, counting the number of contrast-enhancing lesions might suffice. This observation is important when we consider that the assessment of MS disease activity by using serial T2-weighted images is time consuming, requires accurate scan and rescan repositioning, and is characterized by relatively poor intra- and interobserver reproducibility; this last factor is only partly ameliorated with adequate training (29). Higher lesion loads at study entry significantly influenced the frequencies of active lesions during the subsequent 9 months, as well as the observed increases in total lesion volumes. Interestingly, T1-hypointense lesion loads at baseline were only weakly correlated with subsequent T2-hyperintense lesion volume changes; this finding indicated that aggregates of MR-derived parameters might be better for monitoring the evolution of RRMS than individual MR imaging metrics used in isolation (30, 31). These findings also suggest that MR measures reflecting permanent tissue destruction (32) and those reflecting inflammatory MS activity may have different patterns of evolution over short periods of observation.

To better define the main factors influencing RRMS clinical activity during the study period, we performed a multivariate analysis, including both clinical and MR imaging measures as independent variables. We found that both the number of relapses during the previous 2 years and the on-trial contrastenhancing MR depiction of disease activity entered the final multivariable model, achieving the strongest correlation with the occurrence of relapses over the 9 months of the study. All the other MR-derived parameters (number of new T2 lesions during the study period) were excluded from this model, and when patients in the placebo arm were considered in isolation, the results did not change. These data indicate that the recently observed relapse rate, together with the extent of concomitant MR-measured inflammatory activity, is associated with an increased risk of new relapses in patients with RRMS.

We also looked at the correlation between MR lesion load and patients' neurologic disability. At baseline, both T2-hyperintense and T1-hypointense lesion volumes were modestly correlated with patients' EDSS scores. Disappointingly, the strength of the correlation indicated that less than 10% of the observed EDSS variability can be explained by the corresponding MR-measured disease burden. This finding is consistent with the results of several studies of RRMS with similar sample sizes (16, 17). It also indicates that neither abnormal T2-weighted or T1weighted findings are sensitive enough for predicting the disabling aspects of RRMS disease (33). On the other hand, the lack of substantial clinical-MR imaging correlations might also be due to the limitations of EDSS in terms of reliability and responsiveness (25). Our patients had a relatively narrow range of disability at study entry and no notable changes were observed at the end of the study period. As Grimaud et al reported (7), greater variability in neurologic disabilities in selected samples of MS patients (which is reflected by a wider range of EDSS scores) may increase the strength of the relationship with MR imaging findings.

Unexpectedly, in patients treated with GA, a significant, albeit modest, longitudinal correlation was observed between changes in the MR imaging disease burden and the EDSS scores; this was not the case for patients in the placebo group. Given the known effect of GA on MR imaging measures of MS disease burden (22, 31, 34), we believe that this finding might reflect the concomitant lack of clinical changes and the limited increase in lesion volumes in GA-treated patients. However, in patients who received placebos, clinical and MR imaging disease evolution were largely independent of each other.

Conclusion

These study findings confirm that MR-measured MS activity is modestly but significantly correlated with the occurrence of clinical attacks over a short period. Clinical and MR imaging assessments can provide complementary outcome measures for RRMS trials, but MR imaging as a stand-alone measure cannot substitute for clinical assessment in group studies or in individual patient monitoring. Longterm longitudinal studies are still needed to investigate the influence of MR imaging activity on the prognosis and disease evolution in patients with RRMS.

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Appendix: Members of the European/Canadian GA Study Group

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