# Assessing response to interferon-β in a multicenter dataset of patients with MS

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## ABSTRACT

**Objective:** To provide new insights into the role of markers of response to interferon-β therapy in multiple sclerosis (MS) in a multicenter setting, focusing on the relevance of MRI lesions in combination with clinical variables.

**Methods:** A large multicenter clinical dataset was collected within the Magnetic Resonance Imaging in MS (MAGNIMS) network. This included a large cohort of patients with relapsing-remitting MS on interferon-β treatment, MRI and clinical assessments during the first year of treatment, and clinical follow-up of at least 2 additional years. Heterogeneity among centers was assessed before pooling the data. The association of 1-year MRI or clinical relapses with the risk of treatment failure (defined as Expanded Disability Status Scale [EDSS] worsening or treatment switch for inefficacy) and of EDSS worsening alone was evaluated using multivariate Cox models.

**Results:** A pooled dataset of 1,280 patients with relapsing-remitting MS from 9 MAGNIMS centers was analyzed. The risk of failure had a relevant increase with 1 relapse (hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.39–2.44, $p < 0.001$) and ≥3 new T2 lesions (HR 1.55, 95% CI 0.92–2.60, $p = 0.09$). In patients without relapses and less than 3 new T2 lesions, the 3-year risk of failure and EDSS worsening were 17% and 15%; in patients with 1 relapse or ≥3 new T2 lesions, the risks were 27% and 22%; in patients with both conditions or more than 1 relapse, the risks were 48% ($p < 0.001$) and 29% ($p < 0.001$).

**Conclusions:** Substantial MRI activity, particularly if in combination with clinical relapses, during the first year of treatment with interferon-β indicates significant risk of treatment failure and EDSS worsening in the short term. ***Neurology*® 2016;87:134–140**

## GLOSSARY

**CI** = confidence interval; **EDSS** = Expanded Disability Status Scale; **HR** = hazard ratio; **IFN** = interferon; **MAGNIMS** = Magnetic Resonance Imaging in MS; **MS** = multiple sclerosis; **NPV** = negative predictive value; **PPV** = positive predictive value; **RRMS** = relapsing-remitting multiple sclerosis.

Several new and highly active drugs have recently been approved for the treatment of multiple sclerosis (MS), necessitating prompt and informed treatment decisions in patients with suboptimal response to potentially less efficacious treatments. This is difficult due to the inherent uncertainties in defining nonresponse to therapy in a chronic disease such as MS,[1] and complicated by the lack of a standardized definition of the clinical outcomes used to assess worsening of the disease.[2]

Many studies have evaluated the role of clinical and MRI markers to define nonresponders to interferons (IFNs), reporting conflicting results.[3–11] On this basis, a recent meta-analysis aiming at establishing the relevance of MRI markers in predicting a higher risk of disability progression

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failed to combine most of the published studies in a quantitative summary estimate, due to the large heterogeneity in both measured markers and outcome assessments.[12] This heterogeneity precludes a valuable comparison of the different markers and scores of response across different studies.

To provide new insights into the role of markers of response to IFN-β therapy, we analyzed a large multicenter dataset collected within the Magnetic Resonance Imaging in MS (MAGNIMS) network and including a cohort of patients with relapsing-remitting MS (RRMS) on treatment with IFN-β. The aim was to explore whether in patients treated with IFN-β even minimal increases in the number of MRI lesions could be highly predictive of a treatment failure or if a substantial number of new MRI lesions, eventually in combination with clinical relapses, are necessary to best predict IFN-β treatment failure.

## METHODS

**Study population.** The present analysis was run on an integrated dataset including data from 1,890 patients with RRMS treated with IFN-β for at least 1 year (table 1) from 10 MAGNIMS centers. We included retrospectively patients with RRMS treated with any approved preparation of IFN-β as their first therapy, with assessments of Expanded Disability Status Scale (EDSS) score, number of relapses and number of T2 lesions at therapy initiation and after 1 year, and at least yearly clinical assessments, including EDSS score and number of relapses, for a minimum of 2 additional years (3 years from treatment initiation). The allowed time windows for 1-year MRI and clinical examination was 2 months. Dates of treatment switch and reasons for switching, as well as the new drug in case of switch and the last available EDSS assessment and last follow up date, were collected.

**Table 1** Patients included in the analysis and participating centers

| Centers | Patients included, n (%) |
|---|---|
| Rome | 610 (32.3) |
| Milan | 568 (30.1) |
| Barcelona | 233 (12.3) |
| Bari | 120 (6.3) |
| Cagliari | 106 (5.6) |
| Siena | 91 (4.9) |
| Verona | 88 (4.7) |
| Graz | 32 (1.7) |
| Napoli | 27 (1.4) |
| Basel | 14 (0.7) |
| Total | 1,890 (100) |

**Outcome measures.** The definition of treatment failure was based on 2 failure events, whichever occurred first:

1. A confirmed EDSS worsening (according to Rio et al.[1]), here defined and re-estimated for all the included datasets, as ≥1 point EDSS increase (0.5 point if baseline EDSS ≥5.5 and 1.5 points if baseline EDSS = 0) confirmed at the subsequent visit (6 [or 12] months apart [if the 6-month visit is missing]). EDSS at month 12 was used as the starting point to evaluate progression. Since EDSS progression is the final outcome indicating nonresponse to treatment, it was not included in the set of markers of response. Therefore, patients with an EDSS progression during the first year of therapy, if confirmed in subsequent visits, were considered progressed patients at year 1.
2. A switch to other therapies for lack of efficacy. Two fields of the merged dataset were used for this definition: the reason for switching (inefficacy, tolerability, or others) must be inefficacy; the new drug used should be any second-line therapy according to the European Medicine Agencies[13] (http://www.ema.europa.eu/ema/) regulation. Switches among different IFN-βs were not considered as treatment changes if done within a time frame of 1 or 2 months. Otherwise the time to failure was censored at the time of switching.

We also ran the analysis considering all the switches as censored observations and using the time to EDSS worsening as previously defined as the final outcome.

**Standard protocol approvals, registrations, and patient consents.** The original raw data collections were approved by the local ethics committees at all centers and written informed consent was obtained from all study patients.

**Statistical analyses.** Heterogeneity among the MAGNIMS centers was evaluated by grouping centers that enrolled a number of patients <10% of the total (<200 patients).

Heterogeneity in baseline characteristics was evaluated by an analysis of variance model or a $\chi^2$ test, depending on the nature of the evaluated variable. Heterogeneity in 1-year assessments (number of new T2 lesions and number of relapses) was assessed by a negative binomial model. Heterogeneity in time to treatment failure and time to EDSS worsening was assessed by Kaplan-Meier curves and the log-rank test.

Survival analysis methods were used to account for the different follow-up lengths. Before pooling all the datasets, an assessment of heterogeneity regarding the effect of markers assessed at 1 year after treatment start on time to failure was carried out by an interaction test in a multivariate Cox model, with the time to failure from year 1 to the last follow-up as the dependent variable. A significant $p$ value for the interaction test means that there is a relevant heterogeneity among centers in the effect of 1-year markers on time to failure.

In the final model, clinical relapses were entered as a 3-level variable (0, 1, 2, or more) and new T2 lesions as a 7-level variable (0, 1, 2, 3, 4, 5, 6, or more) using a stepwise procedure to check whether both markers are included in the final model and which marker was entered first. Their relative contribution to the risk of failure was evaluated using the relative change in log-likelihood induced by each factor. The best cutoff value for the number of new T2 lesions counted over the first year, leading to an increase in the risk of failure during follow-up, was assessed as the number of lesions causing a relevant change in the hazard ratio (HR) as compared to the reference level (0 new T2 lesions).

The combination of 1-year markers obtained was related to the time of EDSS worsening using a Cox model.

Kaplan-Meier survival curves were used to display the results.

**RESULTS** **Dataset description.** The centers included in the analysis, along with the number of patients provided, are reported in table 1. Baseline characteristics are reported in table 2, with centers grouped as Rome (n = 610), Milan (n = 568), Barcelona (n = 233), and other MAGNIMS centers (n = 479).

Some datasets have been already used in previous publications: the Barcelona dataset and the Milan dataset were both analyzed to validate the Modified Rio Score,[8,9] while the Rome dataset was an updated version of a dataset used to assess the effect of MRI lesions on progression.[5,6]

EDSS was assessed by each center at 6-month intervals.

As expected in a nonrandomized, clinically based population, there were some heterogeneities regarding demographic and clinical characteristics across centers as well as in the number of lesions and relapses detected during the first year of therapy (table 2). This heterogeneity can be accounted for in the main analysis, by adjusting for baseline factors. The proportion of patients with a treatment failure at year 3 after the first year of treatment was homogenous across centers (appendix e-1 and figure e-1 on the *Neurology*® Web site at Neurology.org): the total number of events was 413 (3-year risk of failure 23% [SE 1%]). Also, the proportion of patients with an EDSS worsening at year 3 after the first year of treatment was homogenous across centers (appendix e-1 and figure e-2): the total number of events was 321 (3-year risk of failure 18% [SE 1%]).

**Heterogeneity assessment.** To assess whether the data can be pooled to find the best predictors of treatment failure in a merged dataset, homogeneity of effects was evaluated first. The effect of relapses (adjusted for new T2 lesions) on treatment failure was not significantly heterogeneous across centers ($p$ for interaction = 0.44); the effect of new T2 lesions was highly heterogeneous among centers ($p$ for interaction <0.001). This heterogeneity did not change adjusting the Cox model for all baseline variables (age, sex, baseline EDSS, disease duration). Also, the results remained unchanged when considering the switch for inefficacy as a censored observation rather than an event. The heterogeneity only disappeared when the Rome center was excluded from the analyses. The reasons for this heterogeneity are further explored and the full analysis is reported in appendix e-1, table e-1, and figures e-3–e-5. On the basis of the results of the test for heterogeneity, the Rome center was not included in the pooled analysis.

**Combining the predictors in a score.** In the merged MAGNIMS dataset (n = 1,280), we estimated the average effect of the number of new T2 MRI lesions and relapses during the first year of treatment on risk of failure at follow-up. For completeness, an analysis on how, in the Rome dataset, the presence of relapse or MRI lesions in 1 year of IFN-β can predict risk of failure during follow-up is reported in appendix e-1.

**Table 2** Characteristics of the included patients at treatment start (baseline) and after the first year of treatment

| Center | Age, y, median (range) | EDSS, median (range) | Disease duration,[a] y, median (range) | Relapses previous year, median (range) |
|---|---|---|---|---|
| **Baseline characteristics (treatment start)** | | | | |
| Rome | 31 (10–56) | 1.5 (0–4) | 2.3 (0.0–25.8) | 1 (0–4) |
| Milan | 33 (13–64) | 1.5 (0–5.5) | 3.4 (0.1–33.8) | 2 (0–6) |
| Barcelona | 33 (17–69) | 2 (0–6) | 3.0 (1.0–47.0) | 2 (0–6) |
| Other MAGNIMS | 34 (13–59) | 1.5 (0–5.5) | 2.1 (0–25.6) | 1 (0–5) |
| *p* Value[a] | <0.001 | <0.001 | <0.001 | <0.001 |

| Center | No. of 1-y new T2 lesions, mean (range) | No. of 1-y relapses, mean (range) | Patients with new T2 lesions, % | Patients with relapses, % |
|---|---|---|---|---|
| **Characteristics after 1 y from treatment start** | | | | |
| Rome | 1.1 (0–13) | 0.3 (0–3) | 45 | 25 |
| Milan | 0.7 (0–20) | 0.46 (0–5) | 30 | 32 |
| Barcelona | 1.2 (0–20) | 0.3 (0–4) | 30 | 23 |
| Other MAGNIMS | 0.7 (0–15) | 0.3 (0–5) | 28 | 24 |
| *p* Value[a] | <0.001 | <0.001 | <0.001 | <0.001 |

Abbreviations: EDSS = Expanded Disability Status Scale; MAGNIMS = Magnetic Resonance Imaging in MS.
[a] *p* Value refers to the heterogeneity test across centers.

**Table 3** Multivariate Cox model on the merged MAGNIMS dataset for risk of 3-year treatment failure on 1-year variables (excluding Rome center) (n = 1,280)

| Variables | HR (95% CI) | p Value |
|---|---|---|
| New T2 lesions = 0 | Ref | |
| New T2 lesions = 1 | 0.93 (0.62-1.4) | 0.76 |
| New T2 lesions = 2 | 1.13 (0.73-1.76) | 0.58 |
| New T2 lesions = 3 | 1.55 (0.92-2.60) | 0.09 |
| New T2 lesions = 4 | 2.36 (1.35-4.16) | <0.001 |
| New T2 lesions = 5 | 1.87 (0.81-4.37) | 0.14 |
| New T2 lesions = 6+ | 2.57 (1.53-4.33) | <0.001 |
| Relapse = 0 | Ref | |
| Relapse = 1 | 1.84 (1.39-2.44) | <0.001 |
| Relapse = 2+ | 3.03 (2.06-4.45) | <0.001 |

Abbreviations: CI = confidence interval; HR = hazard ratio; MAGNIMS = Magnetic Resonance Imaging in MS.

To provide quantitative risk estimation according to 1-year clinical and MRI events, we evaluated a global score, based on the optimized cutoffs of new T2 lesions and relapses found in the merged MAGNIMS dataset. In table 3 the HR for relapses (0, 1, 2+) and new T2 lesions (0, 1, 2, 3, 4, 5, 6+) over the first year of therapy are reported. The Cox model shows that the risk of failure significantly increases with 1 relapse (HR 1.84, 95% confidence interval [CI] 1.39–2.44, $p < 0.001$) and with at least 3 new T2 MRI lesions (HR 1.55, 95% CI 0.92–2.60, $p = 0.09$). Relapses were the factor first entered in the model in a stepwise procedure, accounting for 66% of the final log-likelihood change, while new T2 lesions accounted for additional 34% of the total log-likelihood change.

According to these results, risk levels were grouped in 3 classes: group 0 = those without relapses and less than 3 new T2 lesions; group 1 = those with 1 relapse or ≥3 new T2 lesions; group 2 = those with 1 relapse and ≥3 new T2 lesions or ≥2 relapses.

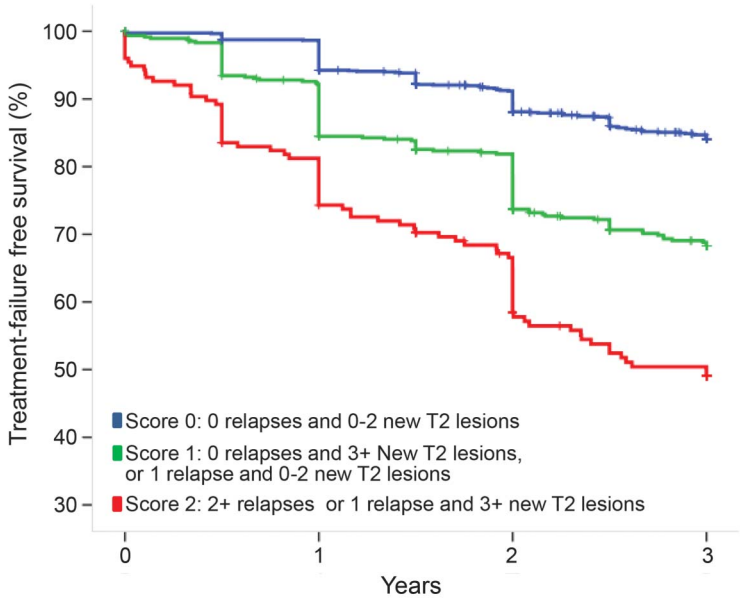
In figure 1, the 3-year risk of treatment failure after 1 year of therapy is reported for patients of the MAGNIMS dataset according to groups described above: patients in group 0 (n = 849, 66%) showed a minimal probability of treatment failure after 3 years (17%); patients in group 1 (n = 301, 24%, HR 1.85, $p < 0.001$) had an intermediate risk of treatment failure over 3 years (27%); patients in group 2 (n = 130, 10%) had a high risk of treatment failure over 3 years (48%, HR 3.81, $p < 0.001$).

Score 0 vs scores 1 or 2 had a positive predictive value (PPV) of 34% and a negative predictive value (NPV) of 83%, a sensitivity of 49%, a specificity of 70%, and a global accuracy of 65%.

The same trend holds true when considering EDSS worsening as the outcome (figure 2): patients in group 0 showed a probability of EDSS worsening after 3 years of 15%, patients in group 1 had an intermediate risk of treatment failure over 3 years (22%, HR 1.52, $p = 0.008$), while those in group 3 have the highest risk of EDSS worsening (29%, HR 2.09, $p < 0.001$).

Score 0 vs scores 1 or 2 had a PPV of 26% and an NPV of 86%, a sensitivity of 50%, a specificity of 70%, and a global accuracy of 66%.

**Figure 1** Treatment failure-free survival




Number at risk:

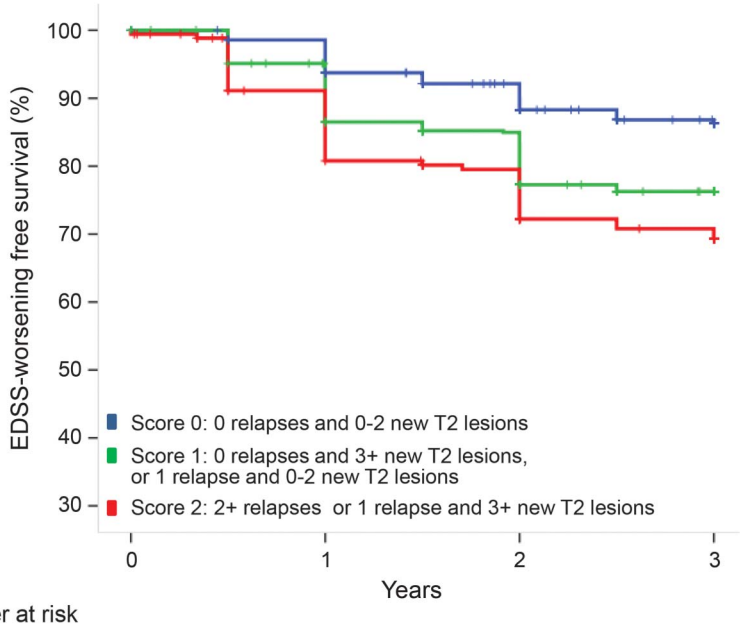
| | | | | |
|---|---|---|---|---|
| Score 0 | 849 | 796 | 684 | 572 |
| Score 1 | 301 | 268 | 222 | 161 |
| Score 2 | 130 | 98 | 76 | 57 |

Treatment failure-free survival over 3 years in the merged Magnetic Resonance Imaging in MS dataset (1,280 patients) following the first year of therapy, according to the different combinations of new T2 lesions and relapses during the first year of therapy grouped in a 3-level score.

**DISCUSSION** The possibility of setting simple rules, based on early detection of MRI lesions and relapses, for defining patients who are not responding to IFN-β therapy has been largely debated.[1–10] The discussion focuses on 2 main issues: Shall we tolerate a degree of disease activity before defining a patient as non-responder to a therapy? In this case, how can we define a cutoff indicating the level of disease activity to be tolerated? Likely, the main limitation for a proper answer to these questions is the lack of consistent evidence on the clinical relevance of the most used outcomes of disease progression, particularly cerebral MRI.

While there is enough consensus on the presence of clinical signs as predictors of nonresponse,[1,14,15] the value of MRI focal lesions in defining response to therapy is less clear. In this context, previous

**Figure 2** Expanded Disability Status Scale (EDSS worsening)–free survival




Number at risk

| | | | | |
|---|---|---|---|---|
| Score 0 | 849 | 796 | 690 | 577 |
| Score 1 | 301 | 276 | 227 | 167 |
| Score 2 | 130 | 112 | 85 | 69 |

EDSS worsening–free survival over 3 years in the merged Magnetic Resonance Imaging in MS dataset (1,280 patients) following the first year of therapy, according to combinations of new T2 lesions and relapses during the first year of therapy groped in a 3-level score.

work[5,6] has shown that 1 new MRI lesion in the first year of therapy, even without any clinical relapse, is enough to highly increase the risk of disability progression thereafter (2–3 years). In contrast, other work based both on experts' consensus[14,15] and on evidence coming from analysis of clinical practice and clinical trial data[1–5,8] has shown that a substantial increase in MRI lesions over 1 year treatment, better with concomitant clinical evidence of disease activity, is required before expecting a consistent increase in the risk of short-term disability progression.

In the present study, we ran a new analysis on a large, multicenter dataset collected within the MAGNIMS network with the final outcome (disability progression) that was uniformly defined. We first realized that it was impossible to pool all the collected data because of an evident heterogeneity in the correlation between MRI lesions and the risk of disability progression, mainly due to the Rome center. This observation was not surprising, since the dominant role of MRI lesions was previously published on the same dataset[5,6] that was just updated for the present analysis. The basic principle for pooling data is the homogeneity of the results to be pooled. Thus, in presence of high heterogeneity, it is better to try to explain it, rather than obtaining an average estimate. We therefore performed additional analyses on the Rome dataset aiming at investigating the reasons for the heterogeneity, which we reposted in appendix e-1.

On the pooled MAGNIMS dataset, the presence of relapses during the first year of IFN-β therapy was the main predictor of the risk of disability progression over the subsequent 3 years. Moreover, the presence of MRI lesions increased the ability to predict disability progression and the cutoff value indicating a substantial risk increase was the presence of at least 3 new T2 lesions. Whereas these results seem to be robust in predicting short-term risk of disability, the scenario could be very different for the long-term risk.[11,16] Additional studies facing this important aim are needed.

It must be stressed here that it is generally difficult to define a universally valid cutoff of MRI lesions. The sensitivity in detecting and counting new lesions depends on many MRI variables,[17,18] which include the acquisition protocol, the frequency of scanning, the time from basal MRI to treatment initiation, and the rater assessing the lesions.[19,20] While in clinical trials there is the attempt to homogenize scanner field strengths, acquisition protocols, frequency of scanning, and even the lesion assessments through a central reading of MRI scans, this is not done in clinical practice and may have an effect on the lesions counted on different MRI sequences, in different periods, and by different raters. In this respect, however, the results reported here are likely to be closer to the clinical practice scenario. In addition, usually cutoffs of MRI lesion numbers do not consider the clinical relevance of the anatomic location of lesion occurrence, as we also did not in the present study. Finally, when assessing therapy response, the occurrence of new lesions should always be interpreted in relation to patient's MRI activity in the recent past and to the time elapsed from the reference scan and the pharmacodynamics of the therapy administered.[12,15,16] The hypothesis of re-baseline of the reference MRI scan after the time necessary for the drug to reach its full effect was proposed previously.[14,15]

This difficulty in indicating a cutoff of MRI lesions that could be valid in all situations is again seen in the present study, where the cutoff of 3 new T2 lesions emerged, which was different from the cutoffs suggested in previous studies, ranging from 1[5] to 5.[8] It is likely, for example, that differences in the MRI lesion cutoffs found between this study and the one we recently published on this topic[8] could lie in the causes of MRI variability described above. What clearly emerges from the present analysis, however, is that the combination of clinical relapses with substantial MRI activity appears as the best predictor of short-term disease progression, whereas minimal MRI activity alone is not. In particular, the present analysis suggests that (1) over the first year of IFN-β

therapy, a low level of MRI activity (i.e., 1–2 new T2 lesions) without clinical relapses produces a negligibly low increase in the risk of clinical worsening in the following 2–3 years (similar to the risk of those who were MRI activity free, 21% vs 19%, $p = 0.58$); (2) over the same period of IFN-β treatment, an increase in the risk of disease worsening is detectable when 1 relapse or substantial MRI activity (i.e., ≥3 new T2 lesions) occurs during the first year of IFN-β therapy (risk of failure around 28%); (3) a high increase in the risk of failure is present when, after 1 year of IFN-β treatment, there is 1 relapse and substantial MRI activity (i.e., ≥3 new T2 lesions) or ≥2 relapses (risk of failure around 48%). These findings can help clinicians evaluate short-term response to IFN-β and therefore guide decisions on switching treatment in patients treated with IFN-β as their first-line therapy for MS.

## AUTHOR CONTRIBUTIONS

M.P. Sormani designed and conceptualized the protocol, analyzed and interpreted the data, ran the statistical analysis, and drafted/revised the manuscript. C. Gasperini and L. Prosperini analyzed and interpreted the data and drafted/revised the manuscript. M. Romeo, J. Rio, M. Calabrese, E. Cocco, C. Enzingher, F. Fazekas, M. Filippi, A. Gallo, L. Kappos, M.G. Marrosu, V. Martinelli, M.A. Rocca, A. Rovira, T. Sprenger, M.L. Stromillo, G. Tedeschi, M. Tintorè, C. Tortorella, M. Trojano, X. Montalban, C. Pozzilli, and G.C. Comi collected the patient data, interpreted the results, and revised the manuscript. N. De Stefano was involved in the protocol design, data acquisition and analysis, and in writing and revising the manuscript.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## DISCLOSURE

M. Sormani has received personal compensation for consulting services and for speaking activities from Genzyme, Merck Serono, Teva, Synthon, Roche, Novartis, and Biogen. C. Gasperini has received compensation for consulting from Bayer HealthCare and Biogen and as a speaker for lectures from Biogen, Bayer HealthCare, Genzyme, Merck Serono, Novartis, and Teva. M. Romeo reports no disclosures relevant to the manuscript. J. Río received compensation for participating on advisory boards from Biogen Idec, Genzyme, and Novartis and received speaker honoraria from Schering-Bayer, Serono, Biogen, and Teva. M. Calabrese has received honoraria from Schering, Biogen-Idec, Teva, Novartis, Genzyme, and Merck Serono S.A. for consulting services, speaking, and travel support. He serves on advisory boards for Schering and Novartis. He has received research grant support from the International Progressive MS Alliance. E. 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