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What is This?
Immunomodulatory therapies delay disease progression in multiple sclerosis

Roberto Bergamaschi¹, Silvana Quaglini², Eleonora Tavazzi¹, Maria Pia Amato³, Damiano Paolicelli⁴, Valentina Zipoli³, Alfredo Romani¹, Carla Tortorella⁴, Emilio Portaccio³, Mariangela D’Onghia⁴, Francesca Garberi², Valeria Bargiggia¹ and Maria Trojano⁴

Abstract

Background: Few studies have analysed long-term effects of immunomodulatory disease modifying drugs (DMDs).

Objective: Assessment of the efficacy of DMDs on long-term evolution of multiple sclerosis, using a Bayesian approach to overcome methodological problems related to open-label studies.

Methods: MS patients from three different Italian multiple sclerosis centres were divided into subgroups according to the presence of treatment in their disease history before the endpoint, which was represented by secondary progression. Patients were stratified on the basis of the risk score BREMS (Bayesian risk estimate for multiple sclerosis), which is able to predict the unfavourable long-term evolution of MS at an early stage.

Results: We analysed data from 1178 patients with a relapsing form of multiple sclerosis at onset and at least 10 years of disease duration, treated (59%) or untreated with DMDs. The risk of secondary progression was significantly lower in patients treated with DMDs, regardless of the initial prognosis predicted by BREMS.

Conclusions: DMDs significantly reduce the risk of multiple sclerosis progression both in patients with initial high-risk and patients with initial low-risk. These findings reinforce the role of DMDs in modifying the natural course of the disease, suggesting that they have a positive effect not only on the inflammatory but also on the neurodegenerative process. The study also confirms the capability of the BREMS score to predict MS evolution.

Keywords

Multiple sclerosis, disease progression, immune therapies, prognosis, clinical research methods, Bayesian analysis

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Introduction

Immune drugs (IDs), in particular disease-modifying drugs (DMDs) such as β-Interferons (IFNs) and glatiramer acetate (GA), changed the natural disease course of multiple sclerosis (MS). DMDs, as largely proven by randomized clinical trials (RCTs), can reduce the risk of new inflammatory events in patients with clinically isolated syndrome (CIS) suggestive of MS¹–⁴ and in relapsing–remitting MS (RRMS).⁵–⁸ However, only open label studies reported the efficacy of DMDs in slowing the long-term progression of the disease⁹–¹² The latter is an important event, albeit difficult to observe with RCTs.¹³ On the other hand, observational studies, which can be used for long-term outcomes, are affected by substantial biases. As a consequence the comparison between heterogeneous groups of treated and untreated patients is difficult. To address this concern, we had defined a risk score (Bayesian risk estimate for MS, BREMS) using a
Bayesian approach and assessed its effectiveness to predict at an early stage the unfavourable long-term evolution of MS.\textsuperscript{14,15} Therefore, in the present study we employ BREMS for analysing observational data of MS patients stratified by their propensity to reach secondary progression (SP), in order to minimize bias in evaluating the effectiveness of DMDs in modifying MS long-term evolution and reducing the risk of reaching SP.

Materials and methods

Patients and variables

We analysed MS patients’ data from three Italian MS centres: Pavia, Northern Italy; Florence, Central Italy; Bari, Southern Italy. We selected patients according to the following inclusion criteria: diagnosis of definite MS according to Poser’s criteria,\textsuperscript{16} initial RRMS course, disease duration $\geq 10$ years, time interval from clinical onset to the first neurological examination $\leq 1$ year.

We selected patients on the basis of Poser’s criteria instead of the more recent ones for two reasons: disease onset in all our patients preceded the statement of the new criteria; Poser’s criteria are more ‘conservative’, and as such are more suitable for selecting patients for observational purposes. Clinical variables are summarized in Table 1.

Patients were divided according to the presence of treatment in their disease history before the endpoint (i.e. reaching SP):

- **Group 1**: Never treated with IDs.
- **Group 2**: Treated with immune therapies of any type, including immunomodulating agents (GA and IFNs), immunosuppressive agents (cyclophosphamide, mitoxantrone, methotrexate, azathioprine), natalizumab and immunoglobulins. We analysed both the whole set of patients in this group and a separate subgroup of patients who received DMDs: GA (Copaxone\textsuperscript{\textregistered} 20 mg subcutaneously every day), or IFN-1b (Betaferon\textsuperscript{\textregistered} 250 µg subcutaneously every other day) or IFN-1a (Avonex\textsuperscript{\textregistered} 30µg intramuscularly once weekly, Rebif\textsuperscript{\textregistered} 22µg subcutaneously three times weekly, Rebif\textsuperscript{\textregistered} 44µg subcutaneously three times weekly), or transient combination therapy (e.g. GA or IFN and mitoxantrone).

We assumed that patients were treated with the most appropriate therapy throughout the course of their disease, considering that neurologists involved in the study are experienced in treating MS; accepted guidelines to make therapy decisions were always used. Therefore, we mainly analysed DMDs as a class of drugs rather than separately, in accordance with Brown et al.,\textsuperscript{9} who considered that this makes it feasible to estimate drug effectiveness for more aggregated subgroups and treatment scenarios. Furthermore, this facilitates the modelling of DMD switches, stops and post-treatment progression paths, which is precluded when DMDs are analysed separately. We considered transient combination therapy (e.g. DMDs and mitoxantrone) to be equal to DMD therapy alone.

The criterion for progressive disease was continuing deterioration (for at least one year) severe enough to lead to an increase of at least one point on EDSS, and confirmed at least one year after onset of progression.\textsuperscript{17, 18} SP onset was assessed retrospectively, at least one year after the onset of the gradual worsening. This was possible because all of the patients included in the study underwent regular neurological examinations. A secondary endpoint was also considered, namely EDSS 6.0 defined as intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 metres with or without resting. Visits were scheduled every six months at least both for treated and untreated patients. Data (clinical events and neurological examination) were collected during each visit, through ad hoc clinical charts, with the same method regardless of the presence of treatment. Treated and untreated patients do not seem to belong to markedly different populations. Indeed, data were collected

<table>
<thead>
<tr>
<th>Variables</th>
<th>First observation</th>
<th>Within first year</th>
<th>Final observation</th>
<th>From onset to final observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>X</td>
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<tr>
<td>Age</td>
<td>X</td>
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<tr>
<td>Neurological symptoms</td>
<td>X</td>
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<tr>
<td>Sequel after the attack</td>
<td>X</td>
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<tr>
<td>Neurological impairment (FSs)</td>
<td>X</td>
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<tr>
<td>Disability (EDSS)</td>
<td>X</td>
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<tr>
<td>N and type of relapses</td>
<td>X</td>
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<tr>
<td>Date of conversion to SP</td>
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<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Disease phase</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use, type, duration of each IT</td>
<td></td>
<td></td>
<td>X</td>
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</tr>
</tbody>
</table>

FSs: Kurtzke’s Functional Systems; EDSS: Expanded Disability Status Scale; SP: secondary progression, defined as the earliest date of observation of a progressive worsening, severe enough to lead to an increase of at least one point on EDSS, and confirmed at least one year after onset of progression;\textsuperscript{17, 18} IT: immune therapy
on patients consequently recruited and followed in the same historical period. The mean disease onset was 22 years ago for treated patients and 26 years ago for untreated subjects, and the median follow-up is 16.5 years for treated subjects and 17.8 for untreated.

The neurological examination was performed by a team of experienced neurologists who underwent training to learn how to properly score and measure the disability of each single functional system. The disability of each functional system was quantified according to the Kurtzke functional system score and a global score according to EDSS was calculated for each patient at each given visit. The data collection was done exclusively by the team of neurologists, without any assistance from pharmaceutical companies. Data collection was performed according to published guidelines. Sex, percentage of patients reaching EDSS 4.0 within the first year of disease course and percentage of patients reaching the endpoint along time was similar in all MS centres involved in the study, so that we could exclude a centre effect affecting the validity of the results. Although statistically different (Kruskal–Wallis analysis of variance p-value <0.01), the variation of the median age in the three centres was in a very narrow range, between 24.5 (Bari patients, inter-quartile range, IQR 19.7–29.9) and 26.4 (Firenze patients, IQR 20.9–34.2) years. Median age of Pavia patients was 25.3 (IQR 20.9–32.6).

The Bayesian risk estimate for MS score

BREMS is the product of our past studies that approached the problem of MS prognosis by using Bayesian statistics. There, using a different data set from the present one, we built a Bayesian graphical model that allowed us to identify clinical factors collected within the first year of disease significantly related to the risk to reach SP. Each prognostic factor was associated to a specific statistical weight, interpretable as a relative risk. Therefore, for each MS patient in the present study, it was possible to calculate, by adding the relative risks of each clinical factor, an individual score whose value was strongly related to the risk to reach SP. BREMS was calculated at the individual patient’s level according to this algorithm: 0.05 × age (in decades) + (−1.07) (if female gender) + 0.93 (if spinal onset) + 0.62 (if pure motor onset) + 0.81 (if motor-sensory onset) + 0.32 × number of neurological functional systems involved at onset + 0.52 (if sequel after onset) + 0.71 × number of sphincter and motor relapses + 0.44 (if EDSS = 4.0 within the first year of disease and outside relapse).

Statistical analysis

We subdivided patients into three groups, on the basis of their propensity to reach SP, which was expressed by the BREMS score calculated during their first year of disease: low risk (BREMS ≤ 25th percentile), high risk (BREMS ≥ 75th percentile) and intermediate risk (BREMS between 25th and 75th percentile). We also performed Receiver Operating Characteristics (ROC) analysis in an attempt to find a cut-off value of BREMS which could discriminate patients with a long-term good or bad prognosis.

We used the Kolmogorov–Smirnov goodness-of-fit test to evaluate all of the continuous variables for normality. None of the variables showed enough good normality, so we used median and inter-quartile range (IQR) for descriptive statistics, and non-parametric tests for comparisons and correlations: Mann–Whitney test for comparing variables between two groups of patients; Kruskal–Wallis rank test for analysis of variance; Spearman’s test to investigate correlation between variables. Chi-square test was used for cross-tabulation analysis.

We used the Kaplan–Meier method to draw survival curves for the main endpoint (time to reach SP), and the log-rank test to calculate the difference between the two survival curves.

We used Cox’s proportional hazards model to test the statistical significance of potential prognostic factors, and we retained only models that satisfied the hypothesis of proportional hazards, which was tested using the Schoenfeld residuals method.

Results

Clinical and demographic features of patients are summarized in Table 2.

Data from 19,401 person-years were analysed pre-progression.

One hundred and forty-three patients (12.1%) reached the endpoint (the shift to SP) within 10 years and 376 patients (31.9%) by the end of the entire observation. The median time to reach SP was 11.9 years (range 1–34.5).

Considering only pre-progression treatments that lasted longer than three months, 700 patients (59.4%) were treated with at least one immune therapy. Four hundred and fifty-nine out of 700 treated patients (65.6%) were treated with only IFN and 41 (5.9%) were treated with only GA. The remaining 478 patients (40.6%) were either treated for less than three months (77 cases that discontinued immune because of adverse events or treatment refusal) or never treated (401 cases, Table 3), except for steroids during relapses and symptomatic drugs.

All patients

We divided patients into two groups on the basis of the clinical course observed over 10 years from disease onset: RR (1035 patients, 87.9%) and SP (143 patients, 12.1%). The median BREMS scores were significantly higher in the subgroup of patients who reached SP within 10 years in
comparison with progression-free patients or patients who reached SP after 10 years: BREMS 0.72 (IQR -0.008–1.26) vs. 0.30 (IQR -0.58–0.95), Wilcoxon test \( p < 0.0001 \). SP-free survival analysis also demonstrated that BREMS was significantly related to SP in the whole cohort (\( p < 0.0001 \)).

ROC analysis, performed with the aim of dividing patients into groups with 'good' and 'bad' prognosis, showed a value of the area under the curve of only 0.65. As the assessment of a cut-off value for BREMS was impossible we divided patients into quartiles, and compared patients with the highest BREMS (fourth quartile, BREMS value ≥ 0.97) with patients with the lowest BREMS (first quartile, BREMS value ≤ -0.56). Among patients with higher BREMS, 17% reached SP within 10 years of disease onset, while only 4.4% of patients with lower BREMS reached SP.

The univariate Cox regression analysis confirmed that higher BREMS value (within the fourth quartile) was significantly related to higher risk of reaching SP (\( p < 0.0001 \)).

### Table 2. Clinical and demographic features of 1178 multiple sclerosis patients, divided into different groups according to the use and type of treatment.

<table>
<thead>
<tr>
<th>( \text{Table 2. Clinical and demographic features of 1178 multiple sclerosis patients, divided into different groups according to the use and type of treatment.} )</th>
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<tbody>
<tr>
<td><strong>Group 1</strong></td>
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<tr>
<td><strong>Untreated patients</strong></td>
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<tr>
<td>Patients: no. and %</td>
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<tr>
<td>Sex: no. and %</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Median age at onset: years and IQR*</td>
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<td>Median disease duration: years and IQR*</td>
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<td>Median BREMS and IQR*</td>
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<td>Median duration of therapy: months and IQR*</td>
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<tr>
<td><strong>Group 2</strong></td>
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<tr>
<td><strong>Treated patients</strong></td>
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<td>Patients: no. and %</td>
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<td>Sex: no. and %</td>
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<td>Male</td>
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<td>Female</td>
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<td>Median age at onset: years and IQR*</td>
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<td>Median disease duration: years and IQR*</td>
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<td>Median BREMS and IQR*</td>
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<tr>
<td>Median duration of therapy: months and IQR*</td>
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<tr>
<td><strong>All patients</strong></td>
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<tr>
<td>Patients: no. and %</td>
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<td>Sex: no. and %</td>
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<td>Male</td>
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<td>Median age at onset: years and IQR*</td>
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<td>Median disease duration: years and IQR*</td>
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<tr>
<td>Median BREMS and IQR*</td>
</tr>
<tr>
<td>Median duration of therapy: months and IQR*</td>
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</tbody>
</table>

*Significant differences (\( p < 0.01 \)) between groups.

### Table 3. List of the explanations for the lack of immune therapies.

<table>
<thead>
<tr>
<th>( \text{Table 3. List of the explanations for the lack of immune therapies.} )</th>
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<tbody>
<tr>
<td><strong>No. of patients (%)</strong></td>
</tr>
<tr>
<td>SP reached before 1996*</td>
</tr>
<tr>
<td>Fear of side effects</td>
</tr>
<tr>
<td>‘Benign’ course*</td>
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<tr>
<td>Planning of pregnancy</td>
</tr>
<tr>
<td>Concomitant diseases</td>
</tr>
<tr>
<td>Unknown reason</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*1996 was the year in which Interferon was admitted for MS therapy by the Italian Health System (glatiramer acetate was admitted later). EDSS ≤ 3.0 during the entire follow-up.

Untreated patients (478 patients)

Clinical course within 10 years was RR in 382 (79.9%) and SP in 96 (20.1%). The median BREMS score was significantly higher in the subgroup of patients who reached SP within 10 years: BREMS 0.77 (IQR -0.03–1.29) vs. 0.26 (IQR -0.58–0.91), Wilcoxon test \( p < 0.0001 \).

The univariate Cox regression analysis comparing patients belonging to the first and the fourth quartiles clearly showed that higher BREMS value was significantly related to higher risk of reaching SP (\( p < 0.000001 \)) (Figure 1).

The probability of reaching SP within 10 years of disease onset was 31.3% in patients with higher BREMS scores, 9.1% in patients with lower BREMS scores. After 20 years, 64.4% of patients who started with a high BREMS score.
A score reached SP, almost triple the number of SP patients who started with a low BREMS score (22.5%).

**Patients treated with immune drugs (700 patients)**

Clinical course within 10 years was RR in 653 (93%) and SP in 47 (7%).

Median BREMS score in patients who reached SP within 10 years was higher than in patients who did not reach SP: BREMS 0.65 (IQR 0.11–1.14) vs. 0.34 (IQR -0.58–0.97), Wilcoxon test $p<0.01$.

**Patients treated with IFN or GA (606 patients).** Clinical course within 10 years was RR in 585 (97%) and SP in 21 (3%).

Median BREMS score in patients who reached SP within 10 years was not significantly different from the subgroup of patients who did not reach the endpoint; BREMS respectively for the subgroups = 0.55 (IQR –0.006–1.37) vs. 0.32 (IQR –0.58–0.95).

**High risk patients (fourth quartile of BREMS): treated versus never treated with DMDs**

Clinical and demographic features are summarized in Table 4.

The number of patients treated with immune drugs other than IFNs or GA was negligible (94 out of 700 patients), therefore we focused further analyses solely on IFNs and GA.

Among the selected high risk patients, treated subjects (148) had a lower risk of reaching SP than untreated subjects (147) ($p<0.000001$, RR 0.231, 95% confidence interval, CI 0.151–0.349) (Figure 2).

After 10 years’ disease duration, 4.1% of the treated patients reached SP versus 31.3% of the untreated patients. After 20 years’ disease duration, 25.4% of the treated patients reached SP versus 64.4% of the untreated patients.

**Low risk patients (first quartile of BREMS): treated versus never treated with DMDs**

Clinical and demographic features are summarized in Table 4.

In this group we found a significantly higher risk of reaching SP in the 137 untreated than in treated patients (158) ($p<0.001$, RR 0.271, 95%CI 0.13–0.556) (Figure 3).
After 10 years’ disease duration, 1.5% of the treated patients reached SP versus 8.1% of the untreated patients. After 20 years’ disease duration, 7.0% of the treated patients reached SP versus 26.5% of the untreated patients.

Impact of BREMS on the predictive model

Cox regression analysis showed that both treatment and BREMS are independently significant predictors of SP-free survival (the explained variance of the model, i.e. the $r^2$ value without BREMS is, 0.106 (Wald test $p$-value < 10^-15), while including BREMS it increases to 0.138 (Wald test $p$-value =< 10^-17). Thus, BREMS increases the explained variance of about 30%).

Secondary endpoint (EDSS 6.0): all of the described results apply also on the secondary endpoint, as shown in Figures 4, 5 and 6.

Discussion

This study used observational data to evaluate whether DMDs modify long-term MS evolution.

Treating MS patients at an early stage with DMDs can delay the conversion from syndromes suggestive of MS onset to clinically definite MS and reduce the relapse rate. An important question that still needs to be addressed concerns whether DMDs also slow disease progression. To date, most data on long-term efficacy of DMDs come from open-label extensions of RCTs in which methodological problems compromise the validity of results. Results from a recent observational study conducted in the UK reported a lack of efficacy of immunomodulatory treatments in slowing the disease progression. The short follow-up and several methodological issues, however, limit the utility of these data in evaluating the efficacy of DMDs on long-term outcomes.
In general, RCTs represent the most rigorous condition for assessing therapeutic efficacy, for the low risk of bias and confounding factors. However, RCTs have some limits such as the length of the observation period, inevitably short for ethical constraints and costs, and the analysed endpoints, generally ‘soft’ or surrogate. In addition, RCT findings are obtained under ‘artificial’ conditions and refer to subpopulations of patients, while treatment decisions must be taken in the ‘real world’ at individual level. In contrast, observational studies analyse large cohorts of patients for long-period follow-up and under ‘real’ conditions but are limited by several biases, mostly due to lack of randomization. An ideal approach should produce reliable results under observational conditions by applying statistical tools able to adjust for such biases. In recent studies a propensity score was employed to adjust analysis by grouping patients with a similar likelihood of receiving therapy. We applied a different approach to reach a similar goal, adjusting our analysis by grouping patients with a similar likelihood of experiencing unfavourable disease evolution. In a previous study we exploited a Bayesian analysis with a Markov chain Monte Carlo simulation to model natural MS history. A Bayesian approach is considered more flexible in the analysis of treatment data, more ethical than traditional methods and provides information useful both for patient-specific decisions and public policy. In recent years the Bayesian methodology has been suggested as an alternative to the frequentist method when dealing with medical problems such as the prognosis of chronic diseases. We used prognostic factors previously selected with the Bayesian model of the natural history of MS to calculate a risk score (BREMS) for each individual patient in the first year of disease. BREMS proved to be a simple and specific tool able to predict long-term evolution of MS at an early stage. Therefore we used BREMS to adjust our analysis by performing an a posteriori subdivision of the patients on the basis of the ‘natural’ propensity for a good or a bad prognosis, minimizing selection bias and confounding factors due to the lack of randomization. This observational cohort, coming from three different Italian centres, was representative of the general MS population in terms of sex, prevalence, age at onset and time elapsed before conversion to SP. In particular, time elapsed before conversion to SP was 17.4 years in our cohort, which is similar to data reported by Tremlett et al. Moreover, the clinical and demographical features were very similar among centres, and a centre effect compromising the validity of the results was excluded.

Our findings show that BREMS values are strongly correlated to long-term disease evolution in terms of SP attainment. This reinforces both the prognostic power and the reliability of BREMS, as indicated by our previous validation studies, and by a meta-analysis of 16 epidemiological studies.

With this study we confirmed that DMDs modify significantly the prognosis of MS.

Previous studies showed that clinical surrogates of unremitting disability, such as EDSS, might be unreliable and present unpredictable variations of the score, leading to difficulties in determining therapy effectiveness. This apparent contradiction can be explained considering that Ebers et al. examined clinical surrogates of clinical disability applied in the context of clinical trials, which are limited, as aforementioned, by the relatively short duration of the study.

Notably, treatment effect does not depend on the initial risk of poor prognosis.

Considering that most MS patients have an ‘intermediate’ course, it was impossible to find a cut-off value for BREMS. Patients were then divided into quartiles and further statistical analyses were performed on the two ‘extreme’ subgroups, characterized by the highest and the lowest risk of unfavourable disease evolution. DMDs favourably modify long-term disease course both in patients with high (fourth quartile) and low (first quartile) BREMS values, indicating that DMDs are beneficial not only for patients who have a high risk of naturally experiencing unfavourable disease evolution, but also for patients who are expected to accumulate only a mild disability. Notably, the same results were obtained with the secondary endpoint (progression to EDSS 6.0).

The recent introduction of new compounds such as natalizumab and fingolimod significantly more powerful than DMDs in reducing clinical and MRI activity, might lead to downplaying the advantages of ‘traditional’ immunomodulatory treatments. However, their safety profile has yet to be fully defined. Therefore the notion that DMDs can impact positively on MS long-term evolution, confirmed with the current study, is still of valuable importance.

In conclusion, the results obtained from observational data analysed with a Bayesian score suggest that immunomodulatory treatments have beneficial effects on the long-term disease evolution of all MS patients. This would strengthen the hypothesis that DMDs not only reduce neuroinflammation but also delay neurodegeneration. Our findings could add further elements to data already available regarding the cost-effectiveness of DMDs.

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**Conflict of interest**

Dr Bergamaschi received: honoraria for speaking from Bayer Schering, Biogen, Novartis, Sanofi-Aventis, Teva; research grants from Bayer Schering, Biogen, Novartis, Sanofi-Aventis, Teva; congress and travel expense compensations from Bayer Schering, Biogen, Novartis, Sanofi-Aventis, Teva.

Professor Quaglini, dr Garberi, dr Romani, dr D’Onghia and Dr Bargiggia have no disclosure to report.
Dr Tavazzi received compensation for consulting from Biogen Idec.

Professor Amato received personal compensation from Merck Serono, Biogen Dompè, Sanofi Aventis, Bayer Schering for serving on scientific advisory board and for speaking. Prof. Amato received financial support for research activities from Merck Serono, Sanofi Aventis, Biogen Dompè, Bayer Schering, Novartis.

Dr Paolicelli received honoraria for consultancy and/or speaking from Biogen Idec, Novartis and Bayer-Schering and research grants from Merck-Serono.

Dr Tortorella has received personal compensation for activities by Biogen Dompè, Bayer Schering, Sanofi Aventis Pharmaceuticals, Merck Serono and Novartis as consultant and speaker.

Dr Zipoli and Dr Portaccio have received research grants from Bayer, Biogen Idec, Merk Serono, Sanofi-Aventis and Novartis.

Dr Trojano received honoraria for consultancy and/or speaking from Biogen Idec, Merck Serono, Sanofi Aventis, Biogen Dompè, Bayer Schering, Novartis and Bayer-Schering and research grants from Merck-Serono, Biogen Idec, Sanofi-Aventis and Novartis.

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