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Original article

MAGNIMS score predicts long-term clinical disease activity-free status and confirmed disability progression in patients treated with subcutaneous interferon beta-1a

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ABSTRACT

Background: Subcutaneous (sc) interferon (IFN) β-1a reduces relapse rates and delays disability progression in patients with MS. We examined the association of the year 1 Magnetic Resonance Imaging in MS (MAGNIMS) score with long-term clinical disease activity (CDA) -free status and confirmed disability progression in patients treated with sc IFN β-1a in PRISMS.

Methods: Patients treated with sc IFN β-1a three-times-weekly (22 or 44 μg; pooled data) were classified by MAGNIMS score (0, $n = 129$; 1, $n = 108$; 2, $n = 130$) at year 1. Hazard ratios (HR; 95% confidence intervals [CI]) for risk of CDA and confirmed Expanded Disability Status Score (EDSS) progression were calculated by MAGNIMS score for up to 15 years of follow-up.

Results: The risk of CDA was higher with a year 1 MAGNIMS score of 1 versus 0 (HR 1.82 [1.38–2.41]), 2 versus 0 (2.63 [2.01–3.45]) and 2 versus 1 (1.45 [1.11–1.89], all $p < 0.0001$). The same outcome was observed with the risk of confirmed EDSS progression (1 versus 0: 1.93 [1.23–3.02]; 2 versus 0: 2.95 [1.95–4.46]; 2 versus 1: 1.53 [1.05–2.23]; all $p < 0.0001$).

Conclusion: In PRISMS, MAGNIMS score at Year 1 predicted risk of CDA and confirmed disability progression in sc IFN β-1a-treated patients over up to 15 years.

PRISMS-15 clinicaltrial.gov identifier: NCT01034644

1. Introduction

Interferon β (IFN β) is a well-established first-line treatment for relapsing-remitting (RR) MS, the most common form of MS (Noseworthy et al., 2000). Early and effective treatment with IFN β delays disease progression, however responses to treatment can differ (Comi et al., 2012; Kappos et al., 2006; Kinkel et al., 2006). Sub-optimal patient response to first-line therapies predicts greater risk of relapse and disability progression (Freedman et al., 2017). It is, therefore, important to determine reliable predictors of treatment response to identify patients who may have a sub-optimal response to a first-line therapy.

Several scores and tools that consider clinical and MRI parameters have been developed to classify patients according to their early response to treatment (e.g. the RIO and modified RIO scores (Rio et al., 2009; Sormani et al., 2013; Freedman et al., 2017)). The Magnetic Resonance Imaging in MS (MAGNIMS) network developed a score that was validated in a real-world, multicentre data set of more than 1200 patients with RRMS treated with interferon β (IFN β) (Sormani et al., 2016). Patients were classified after 1 year of treatment with IFN β for the risk of disease progression according to the occurrence of relapses (0 to ≥2), and new and enlarging T2 lesions (<3 or ≥3) on 12-month MRIs (Sormani et al., 2016). The MAGNIMS score was validated for up to 3

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years in patients receiving IFN β and for up to 7 years in patients receiving teriflunomide (Sormani et al., 2016; Sormani et al., 2017).

The present *post hoc* analysis investigated the potential association between the MAGNIMS score at 1 year and the time to clinical disease activity (CDA) event (disability progression or relapse) and confirmed disability progression in patients treated with subcutaneous (sc) IFN β-1a. Data were obtained from patients who participated in the Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis Study (PRISMS), who were followed for a total of up to 16 years. This allowed the validation of the MAGNIMS score over the longest period to date.

2. Patients and methods

2.1. Patients

The PRISMS-2 double-blind, randomized, placebo-controlled clinical trial, and subsequent follow-ups at years 4 (PRISMS-4), 7–8 (PRISMS-7/8), and 15–16 (PRISMS-15), have been described elsewhere (**Fig. 1**) (PRISMS Study Group, 1998; PRISMS Study Group, 2001; Kappos et al., 2015; Kappos et al., 2006; Oger et al., 2005). Briefly, 560 patients with MS and an Expanded Disability Status Scale (EDSS) score of 0–5.0, from 22 centres in nine different countries were randomly assigned to sc IFN β-1a 22 μg ($n = 189$) or 44 μg ($n = 184$), or placebo ($n = 187$), three times a week (tiw) for two years. Quarterly neurological examinations were performed and patients underwent MRI scans twice a year, with monthly scans in the first nine months (PRISMS Study Group, 1998).

In the 2 year extension study (PRISMS-4), patients who initially received placebo were re-randomized to blinded sc IFN β-1a 22 or 44 μg tiw; while those on active treatment continued blinded treatment with their originally assigned dose. At the beginning of PRISMS-4, 502 of 560 patients originally randomised in PRISMS-2 remained enrolled in the trial (sc IFN β-1a 22 μg, $n = 251$ [84 re-randomized from placebo]; sc IFN β-1a 44 μg, $n = 251$ [87 re-randomized from placebo]). During the 2 year extension period, patients had 3–6 monthly clinical assessments and annual MRI assessments (PRISMS Study Group, 2001).

In PRISMS 7–8, 382 patients (sc IFN β-1a 22 μg, $n = 183$ [60 re-randomized from placebo]; sc IFN β-1a 44 μg, $n = 199$ [63 re-randomized from placebo]) were followed-up. The long-term follow-up (LTFU) assessment comprised a retrospective review of neurologic documentation from the final neurologic visit of PRISMS-4 (Kappos et al., 2006). This included the documentation of relapses, EDSS scores, and whether patients had developed SPMS or not. A further MRI scan was also performed during this visit.

Approximately 15–16 years after the initial randomization, patients from the original PRISMS study were invited to attend a single follow-up visit (PRISMS-15) (Kappos et al., 2015). This was attended by 291 patients (100 patients who originally received placebo, 96 who received sc IFN β-1a 22 μg and 95 who received sc IFN β-1a 44 μg), of whom 290 (51.8%) were analyzed. The visit included a neurological evaluation and a retrospective review of medical history since PRISMS-4 and -7–8.

2.2. Analyses

The present *post hoc* analysis included patients who were initially randomized to sc IFN β-1a 22 μg or 44 μg in the intent-to-treat (ITT) population of PRISMS-2. Data from both sc IFN β-1a arms (22 μg or 44 μg) were pooled for the purposes of this study. Only patients who had year 1 data on T2 lesions and relapses were included in the analysis.

Data from the PRISMS-2, -4, -7/8 and -15 studies were used; each study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation/Good Clinical Practice (GCP) Guidelines, and local regulations. Protocols were approved by health authorities and the relevant independent health committees or institutional review boards, according to country-specific laws. Informed written consent was provided by all patients.

2.3. MAGNIMS scoring categories

The MAGNIMS scoring of patients treated with IFN β has been described previously (Sormani et al., 2016). In the present study, patients who received sc IFN β-1a 22 μg or 44 μg were classified by a MAGNIMS score at year 1. The definitions for each of the MAGNIMS scores (0–2) are shown in **Table 1** (Sormani et al., 2016).

Table 1
MAGNIMS scoring criteria.

MAGNIMS score	Number of new T2 lesions[a]	Number of relapses[a]
0	0–2	0
1	0–2	1
	or ≥ 3	0
2	≥ 0	≥2
	or ≥3	1

[a] T2 lesions and relapses appeared/occurred within the first year of PRISMS-2.

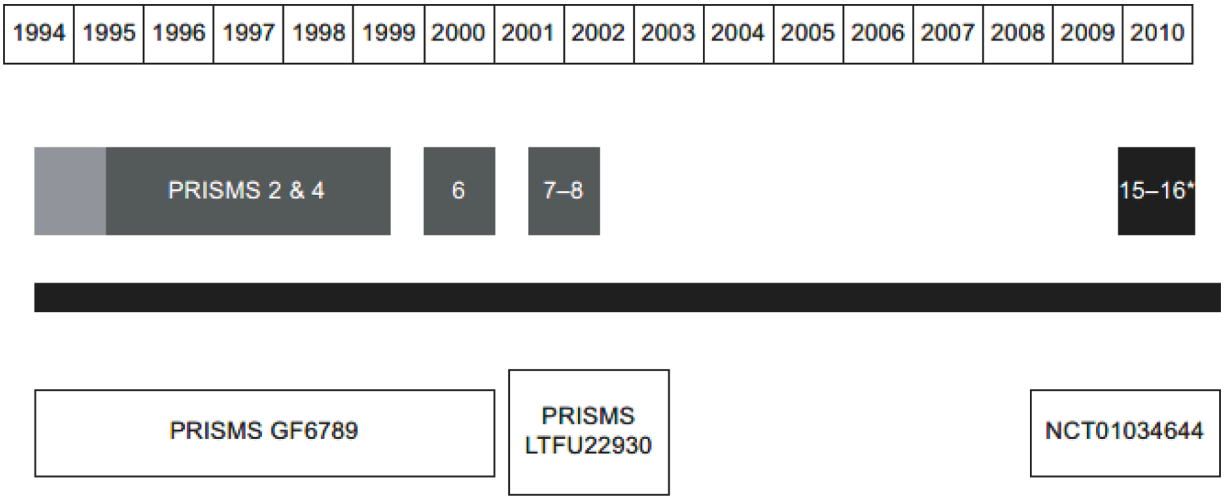

Fig. 1. Schematic of the PRISMS study and extensions. *All patients from the original PRISMS study were invited to attend a single follow-up visit (PRISMS-15), approximately 15–16 years after initial randomisation. LTFU, long-term follow-up; PRISMS, Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis Study.

2.4. Endpoints

The endpoints in this study were time to clinical disease activity (CDA) and confirmed disability progression after 1 year of treatment with sc IFN β-1a. This was evaluated over a 14–15 year time period. CDA-free status was defined as no relapses and no disability progression (i.e. no increase of 1 point from baseline in the EDSS score, or 1.5 points in patients with EDSS 0 confirmed at 3 months). The duration of CDA-free status was calculated from year 1 to the date of first activity. The date of first confirmed EDSS progression was recorded from year 1 to calculate the duration of time without EDSS progression. A disability progression was confirmed if a second disability progression occurred within 75 days of the first.

2.5. Statistical analysis

Median times (95% confidence intervals [CI]) to CDA event and confirmed EDSS progression from year 1 were generated for patients classified by MAGNIMS score. For all sc IFN β-1a-treated patients with non-missing values, Kaplan Meier survival curves were created showing time to CDA event and confirmed EDSS progression after year 1, based on MAGNIMS score at year 1. Treatment switches (and EDSS progression) after Year 1 were not considered as part of the dichotomised event measure at Year 1. Patients who switched treatment after year 1 were censored in the time-to-event analysis. Between-group comparisons were used to assess potential differences in study endpoints between patient groups classified by different MAGNIMS scores, using unadjusted Cox proportional hazards models; hazard ratios (HR) and 95% CIs were calculated. The average yearly change in EDSS from baseline or year 1 to last follow-up visit was estimated using an unstructured repeated-measures mixed model, adjusted for MAGNIMS score after year 1 of therapy and length of follow-up.

2.6. Data availability

Merck KGaA (Darmstadt, Germany) will share patient level, study level data after de-identification, as well as redacted study protocols and clinical study reports from clinical trials in patients. These data will be shared with qualified scientific and medical researchers, upon researcher's request, as necessary for conducting legitimate research. Such requests must be submitted in writing to the company's data sharing portal and will be internally reviewed regarding criteria for researcher qualifications and legitimacy of the research purpose.

3. Results

3.1. Patients

At year 1, a total of 367 patients treated with sc IFN β-1a (22 μg or 44 μg tiw) were available for analysis: 129 patients with a year 1 MAGNIMS score of 0; 108 with a score of 1; and 130 with a score of 2. The number of patients with EDSS progression and confirmed EDSS progression are presented in **Table 2**.

3.2. Clinical disease activity

One hundred CDA events were recorded for patients with a MAGNIMS score of 0; 100 events were recorded for patients with a score of 1, and 119 events for patients with a score of 2 (**Fig. 2**). Using a MAGNIMS score of 0 as a reference, the risk of having a CDA event was significantly higher in patients with MAGNIMS scores of 1 (HR 1.82 [95% CI 1.38–2.41]; $p < 0.0001$]) and 2 (HR 2.63 [95% CI 2.01–3.45]; $p < 0.0001$; Table 3). When comparing a MAGNIMS score of 2 versus 1, the risk of having a CDA event was significantly higher in patients with a MAGNIMS score of 2 (HR 1.45; 95% CI 1.11–1.89; $p < 0.0001$).

The median time to CDA event (i.e. the time taken for 50% of patients to have at least 1 CDA event recorded within the follow-up period) was significantly longer in patients with a year 1 MAGNIMS score of 0 (2.6 [95% CI 2.1–3.6] years) than in patients with scores of 1 (1.6 [95% CI 1.5–1.9] years) or 2 (1.3 [95% CI 1.2–1.4] years). Furthermore, patients with a year 1 MAGNIMS score of 1 had a significantly longer median time to CDA event than those with a score of 2 (non-overlapping 95% CIs).

CDA-Free is defined as no relapses and no confirmed progression of disability. EDSS progression is defined as an increase of 1 point from baseline in the EDSS score, or 1.5 points in patients with an EDSS score of 0. EDSS progression was considered confirmed if a second EDSS progression occurred within a 75 day window of the first. Clinical disease activity and confirmed EDSS progression were calculated after year 1 of the PRISMS study. Patients were given a MAGNIMS score of 0 if they had 0–2 new T2 lesions and 0 relapses; 1 if they had 0–2 new T2 lesions and 1 relapse, or ≥3 new T2 lesions and 0 relapses; 2 if they had ≥0 new T2 lesions + ≥2 relapses, or ≥3 new T2 lesions and 1 relapse. Hazard ratios and 95% CIs are estimated using unadjusted Cox Proportional Hazards Models. A MAGNIMS score of 0 or 1 (as shown) is the reference for all pairwise comparison.

3.3. EDSS progression

Thirty three confirmed EDSS progression events were recorded for patients with a MAGNIMS score of 0, 45 were recorded for patients with a score of 1, and 72 were recorded for patients with a score of 2 (Fig. 3). Using a MAGNIMS score of 0 as a reference, the risk of having confirmed EDSS progression was significantly higher in patients with MAGNIMS scores of 1 (HR 1.93 [95% CI 1.23–3.02]; $p < 0.0001$) and 2 (HR 2.95 [95% CI 1.95–4.46]; $p < 0.0001$; Table 3). When compared with a score of 1, the risk of having EDSS progression was significantly higher in patients with a MAGNIMS score of 2 (HR 1.53; 95% CI 1.05–2.23; $p < 0.0001$).

For the lower MAGNIMS scores at year 1, the median time to confirmed EDSS progression was not reached over the 15–16 year follow-up period and thus cannot be reported. For a year 1 MAGNIMS score of 2, the median time to confirmed EDSS progression was 3.2 (95% CI 2.2–no upper bound) years.

The EDSS course over time during the entire follow-up was significantly affected by the MAGNIMS score at year 1, with the yearly EDSS score change increasing with higher levels of the MAGNIMS score (p for time by MAGNIMS score interaction <0.0001). A significant increase

Table 2
Patients with EDSS progression and confirmed EDSS progression after year 1.

MAGNIMS score	N	Progression n (%)	Confirmed progression[a] n (%)	Unconfirmed progression[b] n (%)	No progression n (%)
0	129	85 (65.9)	33 (25.6)	52 (40.3)	44 (34.1)
1	108	82 (75.9)	45 (41.7)	37 (34.3)	26 (24.1)
2	130	105 (80.8)	72 (55.4)	33 (25.4)	25 (19.2)

[a] EDSS progression was considered confirmed if there was a confirmation progression within a 75-day window of the progression.
[b] Unconfirmed progression was considered unconfirmed if there was no confirmation of progression within a 75-day window of the progression[c]Unknown confirmation means that there was no assessment after baseline for these subjects.

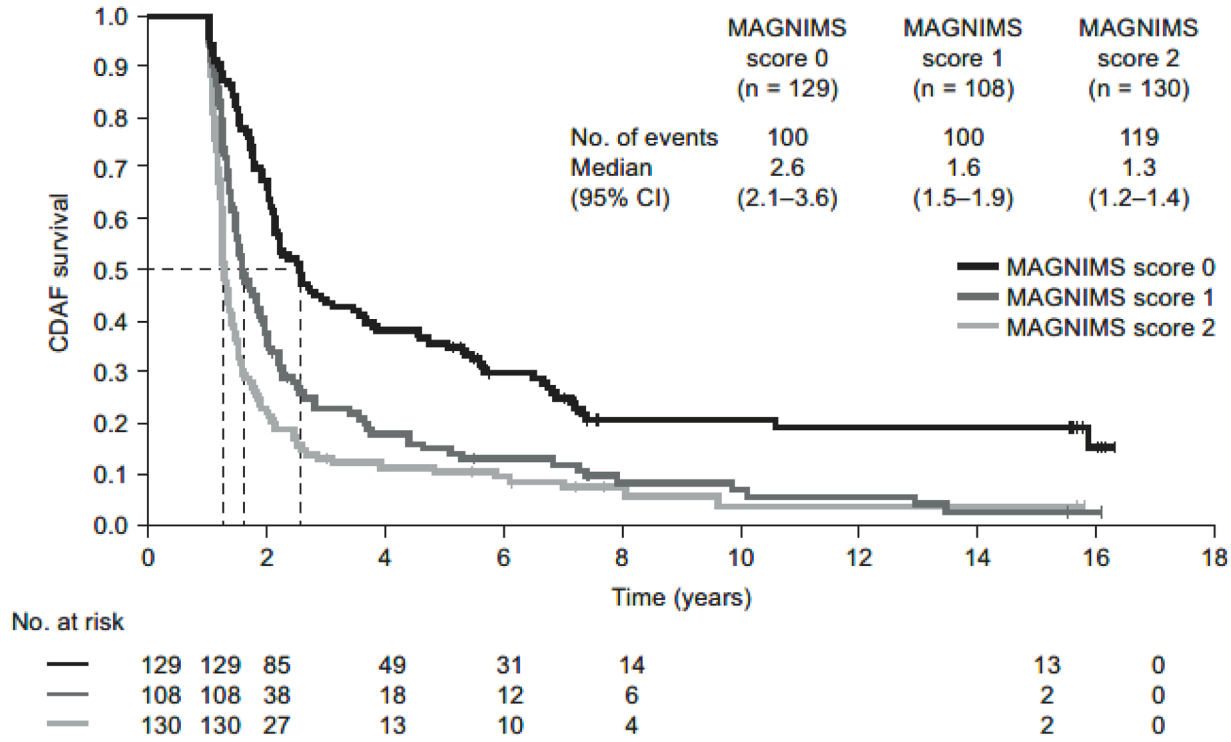

Fig. 2. Kaplan-Meier curve showing time to clinical disease activity after Year 1 by MAGNIMS score in patients treated with sc IFN β-1a (22 or 44 μg) (ITT population). CDA-free is defined as no relapses and no progression of disability. Time to clinical disease activity is based on date of first clinical disease activity event and randomisation date. A significant difference in the time to CDA was observed for all pairwise comparisons of MAGNIMS scores at year 1 (i.e. 1 vs. 0, 2 vs. 0, and 2 vs. 1) since their corresponding 95% CIs did not overlap. Patients were given a MAGNIMS score of 0 if they had 0–2 new T2 lesions and 0 relapses; 1 if they had 0–2 new T2 lesions and 1 relapse, or ≥3 new T2 lesions and 0 relapses; 2 if they had ≥2 relapses, or ≥3 new T2 lesions and 1 relapse. CDAF, clinical disease activity-free; CI, confidence interval; MAGNIMS, Magnetic Resonance Imaging in MS.

Table 3
Hazard ratios for CDA-free and confirmed EDSS progression after year 1 by MAGNIMS score in patients treated with sc IFN β-1a (22 or 44 μg) (ITT population).

Endpoint	Hazard ratio (95% CI)	*P* value
CDA-free		
MAGNIMS 1 vs. 0	1.82 (1.38–2.41)	<0.0001
MAGNIMS 2 vs. 0	2.63 (2.01–3.45)	<0.0001
MAGNIMS 2 vs. 1	1.45 (1.11–1.89)	<0.0001
EDSS Progression		
MAGNIMS 1 vs. 0	1.93 (1.23–3.02)	<0.0001
MAGNIMS 2 vs. 0	2.95 (1.95–4.46)	<0.0001
MAGNIMS 2 vs. 1	1.53 (1.05–2.23)	<0.0001

was observed in patients with MAGNIMS scores of 0, 1 and 2 ($p < 0.0001$; Table 4). From baseline to last follow-up, the average yearly change in EDSS score (95% CI) was highest in patients with a year 1 MAGNIMS score of 2 ($n = 130$; 0.138 [0.128–0.148]) and lowest in patients with a year 1 MAGNIMS score of 0 ($n = 129$; 0.106 [0.097–0.116]; Table 4).

A significant increase in the yearly average EDSS score from year 1 to the last follow-up visit was observed for each MAGNIMS score (all values $p < 0.0001$; Table 5).

Average yearly change in EDSS from baseline to the last follow-up visit is presented. Length of follow-up was between baseline and the last follow-up visit. Patients were given a MAGNIMS score of 0 if they had 0–2 new T2 lesions and 0 relapses; 1 if they had 0–2 new T2 lesions and 1 relapse, or ≥3 new T2 lesions and 0 relapses; 2 if they had ≥0 new T2 lesions and ≥2 relapses, or ≥3 new T2 lesions and 1 relapse. Average yearly EDSS change was estimated using an unstructured repeated−measures mixed model with all EDSS visits considered and patient as the random factor, adjusted for MAGNIMS score after 1 year of therapy and length of follow-up.

Average yearly change in EDSS from year 1 to the last follow-up visit is presented. Length of follow-up was between Year 1 and the last follow-up visit. The year 1 EDSS values are the latest non-missing values that were obtained between days 345 to 385 of the PRISMS study. Patients were given a MAGNIMS score of 0 if they had 0–2 new T2 lesions and 0 relapses; 1 if they had 0–2 new T2 lesions and 1 relapse, or ≥3 new T2 lesions and 0 relapses; 2 if they had ≥0 new T2 lesions and ≥2 relapses, or ≥3 new T2 lesions and 1 relapse. Average yearly EDSS change was estimated using an unstructured repeated−measures mixed model with all EDSS visits considered and patient as the random factor, adjusted for MAGNIMS score after 1 year of therapy and length of follow-up.

4. Discussion

Reliable predictors of treatment outcomes would be useful tools for clinicians when making treatment decisions for patients with MS. Decisions made at an earlier stage of the disease course can prevent disease activity and improve long-term outcomes (Comi et al., 2017). In this study, the MAGNIMS score at year 1 predicted time to, and risk, of a CDA event or confirmed disability progression in patients treated with sc IFN β-1a over a 14 year period.

Prior to this study, the use of MAGNIMS scoring to predict treatment response with IFN β was validated over a relatively short-term timeframe (3 years) (Sormani et al., 2016). Our results also support a previous study of patients treated with teriflunomide, in which a lower MAGNIMS score at year 1 was associated with a significantly lower risk of disability worsening than higher MAGNIMS scores over 7 years. (Sormani et al., 2017) Our analyses extend the observation period to 14–15 years, representing the longest prediction of disease worsening to date and demonstrate the of the utility of the MAGNIMS score for

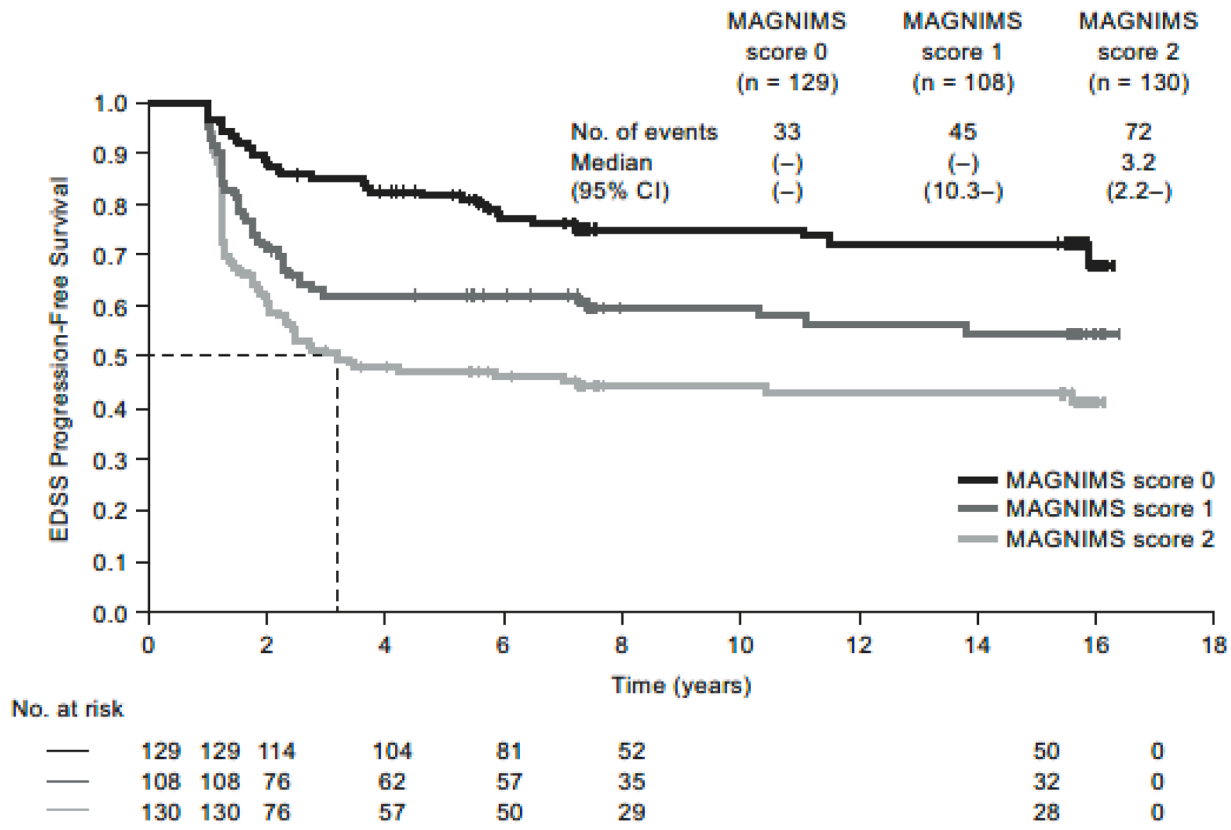

Fig. 3. Kaplan-Meier curve showing time to confirmed EDSS progression after Year 1 by MAGNIMS score in patients treated with sc IFN β-1a (22 or 44 μg; ITT population). EDSS progression is defined as an increase of 1 point from baseline in the EDSS score, or 1.5 points in patients with an EDSS score of 0. EDSS progression was considered confirmed if a second EDSS progression occurred within a 75 day window of the first progression. Time to confirmed EDSS progression is based on the date of the first EDSS progression event and the randomisation date. Patients were given a MAGNIMS score of 0 if they had 0–2 new T2 lesions and 0 relapses; 1 if they had 0–2 new T2 lesions and 1 relapse, or ≥3 new T2 lesions and 0 relapses; 2 if they had ≥0 new T2 lesions and ≥2 relapses, or ≥3 new T2 lesions and 1 relapse. CI, confidence interval; EDSS, Expanded Disability Status Scale; MAGNIMS, Magnetic Resonance Imaging in MS.

Table 4
Average yearly change in EDSS from baseline to follow-up according to MAGNIMS score at 1 year in patients treated with sc IFN β-1a.

MAGNIMS Score	Number of patients	Estimate of EDSS change (95% CI)	*P* value
0	129	0.106 (0.097–0.116)	<0.0001
1	108	0.123 (0.113–0.133)	<0.0001
2	130	0.138 (0.128–0.148)	<0.0001

Table 5
Average yearly change in EDSS from Year 1 to follow-up according to MAGNIMS score at 1 year in patients treated with sc IFN β-1a.

MAGNIMS Score	Number of patients	Estimate of EDSS change(95% CI)	*P* value
0	123	0.109 (0.098–0.120)	<0.0001
1	99	0.128 (0.117–0.139)	<0.0001
2	120	0.123 (0.112–0.134)	<0.0001

predicting time to and risk of CDA, in addition to confirmed disease progression.

In the present analysis, CDA-free status was included as an endpoint in favour of no evidence of disease activity (NEDA). NEDA is a widely used composite endpoint of measures of disease activity, defined as no relapses, disability worsening, gadolinium-enhancing lesions, and new or enlarging T2 hyperintense lesions (Giovannoni et al., 2015). However, the use of NEDA as an endpoint in the present analysis was not feasible, since MRI data were not consistently collected throughout the 15–16 year PRISMS extension data evaluation.

In the previous validation of MAGNIMS scoring criteria in IFN β-treated patients, treatment failure was defined as EDSS worsening or a treatment switch due to inefficacy (Sormani et al., 2016). In the current analysis the definition of treatment failure as a CDA event was modified to either confirmed EDSS worsening, or a switch to second-line therapies or treatment discontinuation due to disease progression. This modification was required since the original definition was difficult to replicate in the PRISMS clinical setting. However, only six patients switched treatment over the course of the PRISMS study; thus the majority of events presented were due to relapse or EDSS progression.

Our analysis was subject to some limitations, in part due to the nature of it being a *post hoc* study design. In addition, the length of the extended follow-up period increases the potential for inconsistency of data collection for relapses and EDSS scores, and the loss of patients to follow-up. Patients who suffered worse outcomes were more likely to terminate participation in the study due to an apparent lack of treatment efficacy which could have potentially skewed the results. Overall, the study had sufficient power to be able to demonstrate statistically significant results for all outcomes measured.

5. Conclusion

The assessment of treatment response by combining the analysis of both clinical and MRI changes during the first year of therapy may be predictive of future events. In the PRISMS study population, the MAGNIMS score at year 1 was able to predict the risk of a CDA event or disability progression in patients treated with sc IFN β-1a over the following 14–15 years. Thus, the MAGNIMS score at year 1 may be a

useful predictor of patients' response to treatment with sc IFN β-1a in the long-term, helping to identify patients with likelihood of more active disease who may benefit from an adjustment of their treatment.

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CRediT authorship contribution statement

Maria Pia Sormani: Conceptualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Mark S. Freedman:** Conceptualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Julie Aldridge:** Conceptualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Kurt Marhardt:** Conceptualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Ludwig Kappos:** Conceptualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Nicola De Stefano:** Conceptualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

MPS has received consulting fees from Biogen, Merck KGaA (Darmstadt, Germany), Teva, Genzyme, Roche, Novartis, GeNeuro and Medday.

MSF has received honoraria or consultation fees from Actelion, Bayer HealthCare, Biogen, Chugai, Merck KGaA (Darmstadt, Germany), Genzyme, Hoffman La Roche, Novartis, Sanofi, Teva.

JA is an employee of EMD Serono Research and Development Institute Inc., a business of Merck KGaA, Darmstadt, Germany.

KM is an employee of Merck Gesellschaft mbH Austria, a business of Merck KGaA, Darmstadt, Germany.

LKs´ institution (University Hospital Basel) has received in the last 3 years and used exclusively for research support: steering committee, advisory board, and consultancy fees (Actelion, Addex, Bayer HealthCare, Biogen, Biotica, Genzyme, Lilly, Merck KGaA [Darmstadt, Germany], Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB, and Xenoport); speaker fees (Bayer HealthCare, Biogen, Merck KGaA [Darmstadt, Germany], Novartis, Sanofi, and Teva); support of educational activities (Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck KGaA [Darmstadt, Germany], Novartis, Sanofi, and Teva); license fees for Neurostatus products; and grants (Bayer HealthCare, Biogen, European Union, Innoswiss, Merck KGaA [Darmstadt, Germany], Novartis, Roche Research Foundation, Swiss MS Society, and Swiss National Research Foundation).

NDeS is a consultant for Schering, Biogen, Teva, Novartis, Sanofi-Genzyme, Roche, and Merck KGaA (Darmstadt, Germany); has grants or grants pending from FISM and Novartis, is on the speakers bureaus of Biogen-Idec, Teva, Novartis, Sanofi-Genzyme, Roche, and Merck KGaA (Darmstadt, Germany); has received travel funds from Teva, Novartis, Sanofi-Genzyme, Roche, and Merck KGaA (Darmstadt, Germany).

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