doi:10.1093/brain/awx185 BRAIN 2017: 140; 2426–2443 | 2426

BRAIN
A JOURNAL OF NEUROLOGY

Towards personalized therapy for multiple sclerosis: prediction of individual treatment response

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Timely initiation of effective therapy is crucial for preventing disability in multiple sclerosis; however, treatment response varies greatly among patients. Comprehensive predictive models of individual treatment response are lacking. Our aims were: (i) to develop predictive algorithms for individual treatment response using demographic, clinical and paraclinical predictors in patients with multiple sclerosis; and (ii) to evaluate accuracy, and internal and external validity of these algorithms. This study evaluated 27 demographic, clinical and paraclinical predictors of individual response to seven disease-modifying therapies in MSBase, a large global cohort study. Treatment response was analysed separately for disability progression, disability regression, relapse frequency, conversion to secondary progressive disease, change in the cumulative disease burden, and the probability of treatment discontinuation. Multivariable survival and generalized linear models were used, together with the principal component analysis to reduce model dimensionality and prevent overparameterization. Accuracy of the individual prediction was tested and its internal validity was evaluated in a separate, non-overlapping cohort. External validity was evaluated in a geographically distinct cohort, the Swedish Multiple Sclerosis Registry. In the training cohort ($n = 8513$), the most prominent modifiers of treatment response comprised age, disease duration, disease course, previous relapse activity, disability, predominant relapse phenotype and previous therapy. Importantly, the magnitude and direction of the associations varied among therapies and disease outcomes. Higher probability of disability progression during treatment with injectable therapies was predominantly associated with a greater disability at treatment start and the previous therapy. For fingolimod, natalizumab or mitoxantrone, it was mainly associated with lower pretreatment relapse activity. The probability of disability regression was predominantly associated with pre-baseline disability, therapy and relapse activity. Relapse incidence was associated with pretreatment relapse activity, age and relapsing disease course, with the strength of these associations varying among therapies. Accuracy and internal validity ($n = 1196$) of the resulting predictive models was high (>80%) for relapse incidence during the first year and for disability outcomes, moderate for relapse incidence in Years 2–4 and for the change in the cumulative disease burden, and low for conversion to secondary progressive disease and treatment discontinuation. External validation showed similar results, demonstrating high external validity for disability and relapse outcomes, moderate external validity for cumulative disease burden and low external validity for conversion to

Received February 7, 2017. Revised June 12, 2017. Accepted June 20, 2017. Advance Access publication August 3, 2017

secondary progressive disease and treatment discontinuation. We conclude that demographic, clinical and paraclinical information helps predict individual response to disease-modifying therapies at the time of their commencement.

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Keywords: multiple sclerosis; prediction; disability; relapses; precision medicine

Abbreviations: ΔAUC = change in the area under curve; DMT = disease-modifying therapy; EDSS = Extended Disability Status Scale

Introduction

Multiple sclerosis is the second most common cause of disability in young adults and is associated with significant societal costs (Noseworthy *et al.*, 2000). At the present time, no neuroregenerative or remyelinating therapies are available for clinical use and so the core of multiple sclerosis management lies in preventing episodic inflammation and relapse-related disability accrual.

Despite the rapid development of multiple sclerosis pharmacotherapy over the past 5 years, prevention of disability in patients with multiple sclerosis has been suboptimal. The most effective of the available immunotherapies mitigate the short-term risk of disability progression by 30–42% (Wingerchuk and Carter, 2014). This imperfect result is mainly attributed to the large interindividual variability in the clinical multiple sclerosis phenotype and the treatment response (Hegen *et al.*, 2016). From the patients' perspective, the time while exposed to multiple sclerosis disease-modifying therapies (DMTs) with a suboptimal individual effect translates into ongoing loss of capacity. While an enormous effort is being invested into developing new, more potent DMTs for multiple sclerosis, it is of paramount importance that use of the currently available DMTs is optimized. Therefore, accurate and timely detection of individual response to these DMTs is an essential requisite of efficient personalized multiple sclerosis therapy. Even though prediction of individual disease course has now become feasible (Tintore *et al.*, 2015; Spelman *et al.*, 2016), prediction of individual treatment response remains an area of unmet need.

'Real-world' data have now established their role in the evaluation of the effectiveness and safety of multiple sclerosis DMTs (Kalincik and Butzkueven, 2016). Large representative observational cohorts systematically followed for long intervals of time provide a unique opportunity to decipher the patterns of disease phenotypes, which act as modifiers of treatment effect and are indicative of individual responsiveness to therapy (Waldman and Terzic, 2016).

In this study, we used MSBase, a global multiple sclerosis cohort study to evaluate demographic, clinical and simple paraclinical predictors (treatment) of future response to DMTs for multiple sclerosis and to develop a predictive algorithm applicable in clinical practice.

Materials and methods

Ethics statement

The MSBase cohort study (Butzkueven *et al.*, 2006) (registered with WHO ICTRP, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee, and by the local ethics committees in all participating centres (or exemptions granted, according to applicable local laws and regulations). Written informed consent was obtained from enrolled patients as required.

Study design

This study evaluated demographic, clinical and paraclinical predictors of treatment outcomes (confirmed progression or regression of disability, relapse incidence, conversion to secondary progressive multiple sclerosis, change in the cumulative disease burden, and DMT discontinuation) at the time of initiating new DMT. All eligible patients from the global MSBase cohort who had commenced a new DMT during the prospectively recorded follow-up were included. Forty-two models (one for each combination of DMT and outcome) were built. The models were applied in prediction of treatment outcomes in individual patients and their accuracy was evaluated. Internal validity was established in a separate, non-overlapping MSBase cohort. External validity was established in the Swedish Multiple Sclerosis Registry (Hillert and Stawiarz, 2015).

Patients and follow-up

Longitudinal demographic, clinical, and paraclinical data from 117 multiple sclerosis centres in 34 countries were extracted from the MSBase cohort study in November 2015. Patients were enrolled based on the following inclusion criteria: diagnosis of multiple sclerosis or clinically isolated syndrome based on the 2005 or 2010 revised McDonald criteria (Polman *et al.*, 2005, 2011), commencement of an index DMT during the prospectively recorded follow-up (irrespective of their previous exposure to DMTs), minimum pre-DMT follow-up of 6 months (with the exception of the patients with <6-month disease duration), minimum on-treatment prospective follow-up of 6 months, availability of the minimum dataset [i.e. patient sex, year of birth, year of the first clinical presentation, disease course, treating centre and at least two clinical visits with recorded Extended Disability Status Scale (EDSS) scores], and a disability score (EDSS) recorded between 6 months prior to and 1 month following the index DMT commencement. Patients with inactive primary progressive multiple sclerosis were excluded (Lublin *et al.*, 2014). Objective data quality assessment was conducted using a data quality and generalizability process identifying any incomplete, invalid or inconsistent entries (Kalincik *et al.*, 2017) (Supplementary Table 1).

The analysed data were recorded as part of quality clinical practice, mostly at large tertiary multiple sclerosis centres, typically with near-real time data entry (at the time of clinical visits). The MSBase protocol stipulates minimum annual updates of the minimum dataset, but patients with less frequent visits were not excluded from the analysis. Data entry portal was either the iMed patient record system or the MSBase online data entry system. The prospective follow-up was defined as the time between the first and the last EDSS entries (which typically coincide with objective neurological assessment).

Disability was assessed by the treating neurologists using EDSS, with Neurostatus certification required at each centre (Kurtzke, 1983). Relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 h, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse (Schumacher *et al.*, 1965). Disease course was evaluated using the diagnostic criteria by Lublin and colleagues (2014).

The results of MRI acquired up to 2 years before the DMT commencement were included. Brain and spinal cord MRIs

were reviewed by the treating physicians at each participating centre and qualitative results were recorded (normal/abnormal-multiple sclerosis/abnormal non-multiple sclerosis). Further more, presence/absence of any contrast-enhancing lesions or new hyperintense T_2 lesions on brain and spinal cord MRIs was recorded.

Qualitative results of a CSF analysis prior to the DMT commencement were reported by treating physicians as normal/abnormal-multiple sclerosis/abnormal non-multiple sclerosis.

Study outcomes

For each therapy, only outcomes recorded during a treated period (i.e. between treatment commencement and treatment cessation or the last recorded EDSS entry, whichever occurred first) were taken into account. Progression of disability was defined as increase in EDSS score by 1.5 steps if previous EDSS was 0, increase by 1 step if previous EDSS was 1–5.5 and increase by 0.5 steps if previous EDSS was $\geqslant 6$. Only the progression events confirmed over $\geqslant 6$ months (with the confirmation EDSS recorded >30 days following a previous relapse and irrespective of treatment status at the time of confirmation) and sustained for the duration of the follow-up were considered (Kalincik *et al.*, 2015*a*).

Similar to the disability progression, regression of disability was defined in three strata (decrease in EDSS by 1.5 steps if EDSS was ≤ 1.5, 1 step if EDSS was 2–6 and 0.5 step if EDSS was $\geqslant 6.5$), confirmed over $\geqslant 6$ months and sustained for the duration of the follow-up.

Relapses, including dates of onset, were recorded.

Conversion to secondary progressive multiple sclerosis was evaluated among patients diagnosed with clinically isolated syndrome or relapsing-remitting multiple sclerosis using an objective definition developed and validated in the MSBase cohort (Lorscheider *et al.*, 2016). The definition requires disability progression by 1 EDSS step in patients with EDSS ≤ 5.5 or 0.5 EDSS steps in patients with EDSS $\geqslant 6$ in the absence of a relapse, a minimum EDSS score of 4, a minimum pyramidal functional system score of 2, and confirmed progression over $\geqslant 3$ months, including confirmation with the leading functional system score.

Change in the cumulative disease burden (due to both flux in disability and multiple sclerosis relapses) was quantified as the annualized change in the area under EDSS-time curve relative to the pre-DMT EDSS score (ΔAUC) (Liu and Blumhardt, 2000; Kalincik *et al.*, 2015*b*).

Discontinuation dates of DMTs were recorded.

Statistical analysis

Statistical analyses were carried out using R, version 3.0.3 (R Development Core Team, 2011). The point and interval estimates of data distributions were expressed as means with 95% confidence intervals, or medians with interquartile range, as appropriate.

The analysis was completed in three stages. First, a series of predictive models were built using training cohorts, which for each therapy consisted of 90% of the eligible patients. A predictive model was designed for each DMT (using a subgroup commencing the corresponding DMT during the prospective follow-up) and study outcome (see above). Patients who successively commenced multiple treatments were allowed to contribute to models for multiple therapies but a maximum of one entry per patient was allowed in each model. The association of a recent treatment switch and its likely reason with disease activity on the current index DMT was accounted for by including in the models the patients' previous treatment status and on-treatment disease activity. Second, internal validity of the predictive models was tested in independent, non-overlapping testing cohorts that consisted of 10% of the eligible patients for each DMT. Third, external validity of the predictive models developed in the training MSBase cohorts were applied in an independent cohort consisting of all eligible patients commencing the respective therapies in the Swedish Multiple Sclerosis Registry.

The probabilities of experiencing on-treatment disability progression, disability regression, or relapses and their determinants were evaluated with a series of univariate marginal proportional hazards models (Andersen-Gill models with one variable per model and cluster term for patient). The probabilities of conversion to secondary progressive multiple sclerosis, or discontinuing therapy and their determinants were evaluated with a series of univariate Cox proportional hazards models. The hazard function for each survival model was estimated as:

$$\hat{S}_i(t) = e^{(-\hat{A}_0(t))^{e(x_i'\hat{\beta})}} \quad (1)$$

where S_i represents the cumulative hazard of event at time t, x_i is the vector of principal components, β is the vector of coefficients estimated by maximizing partial likelihood and A_0 is the baseline hazard function. The baseline hazard function was estimated with the Nelson-Aalen non-parametric estimator of the hazard function:

$$\hat{A}_0(t) = \sum_{j:t_j \leq t} \frac{d_j}{r_j} \quad (2)$$

where d_i is the number of events and r_i is the number of patients at risk at t_i (Nelson, 1972). The proportional hazards assumption was tested by evaluating Schoenfeld residuals and where violated the coefficients were excluded. The candidate predictor variables are shown in Table 2. The relationship between ΔAUC and its potential determinants was evaluated with a series of univariate linear regression models.

Multivariable analyses of the study outcomes were conducted using the models as described above, including all the potential determinants of multiple sclerosis outcomes. Dimensionality of the multivariable analyses was reduced by a non-linear principal component analysis (package 'homals') in the pooled training cohort, including categorical and continuous variables, with components identified by an eigenvalue >0.001, explaining $>5\%$ of the variance in the model, and containing at least two variables with loadings >0.1. Non-linear principal component analysis is a homogeneity analysis with restrictions on its quantification matrix, which uses non-linear transformations (i.e. categorization) of the observed variables (de Leeuw and Mair, 2009). The criterion of minimizing the departure from homogeneity is measured by a loss function, which in 'homals' is based on indicator matrices of binary dummy variables for the number of variable levels $\times$ the number of observations. This structure allows for data missingness and as a result, values of the principal components can be estimated even for patients with incomplete data (de Leeuw and Mair, 2009).

The calculated principal components were used as independent predictors of cumulative hazards or ΔAUC in the multivariable models. In addition to the principal components for the treatment effect modifiers of interest, two 'adjustment components' were defined using the variables specific to the training cohort–multiple sclerosis centre, treatment start date, frequency of the on-treatment visits, and the number of recorded pretreatment EDSS scores, in order to mitigate the confounding associated with the variability in local clinical practice and the flux in diagnostic and management strategies. As a result, each multivariable model of study outcomes consisted of three principal components, two adjustment components and an error term. Compound symmetry covariance structure was used, given the use of the Andersen-Gill models and the orthogonality of the principal components (Supplementary Fig. 3).

Predictive modelling of treatment outcomes in individual patients

A predictive model was built for every combination of the seven studied DMTs and the six defined treatment outcomes for which sufficient information was available in the training cohort. The structure of the predictive models corresponded to the structure of the models described above. The individual probabilities of the outcomes were estimated using the β coefficients and the error terms estimated for the three principal components by the above described multivariable models (excluding the 'adjustment components' as these were not available for the prediction of outcomes). The accuracy of the predictions was assessed in the training cohort and the internal validity was evaluated in the testing cohort, comparing the estimated outcomes to the observed outcomes for every patient. External validity of the predictive models was evaluated in the Swedish Multiple Sclerosis Cohort.

The individual value of the principal components was reconstructed for each patient using the loadings generated by the principal component analysis and individual values of the contributing variables. The values of the principal components were then substituted into the predictive models in order to calculate mean estimated hazard of the study outcomes or the mean ΔAUC over the following 4 years, and their 95% prediction intervals, for each individual patient.

For the repeated events (disability progression, disability regression, or relapses), the predictive accuracy and validity at each year was quantified as the proportion of patients in whom the observed number of events was equal to predicted mean rounded to the nearest integer (where that integer was $\leq$0.33 points from the predicted mean) or either of the two neighbouring integers (where the predicted mean was $>$0.33 points from either integer). For the unique events (conversion to secondary progressive multiple sclerosis or discontinuation of DMT), the prediction accuracy and validity at each year was quantified using the Harrell's C (with the area under the curve for the receiver operation characteristic converted into percentage). For ΔAUC, accuracy and validity at each year was quantified as the proportion of patients with the observed ΔAUC falling within the interval determined by the lower and the greater half-integer nearest to the predicted mean ΔAUC.

Results

Patients and follow-up

Overall, 9193 patients with cumulative prospective follow-up of 81 933 patient-years (mean 9.0 years, median 8.1 years, quartiles 5.0–12.0 years) fulfilled the inclusion criteria (Supplementary Figs 1, 2 and Supplementary Table 2 show patient disposition by DMT, centre, and start and end of the analysed on-treatment period, respectively). The sample was representative of the population treated in tertiary multiple sclerosis centres, with 72% of the patients being female, median age at switching therapy of 38 years, time from the first clinical multiple sclerosis presentation of 7 years and median EDSS score of 2.5 (Table 1). The pooled training cohort included 8513 patients and the testing cohort consisted of 1196 patients of similar characteristics (Table 1). The former was used to develop the predictive models and test their individual predictive accuracy, and the latter was used to assess their internal validity. Characteristics of training cohort stratified by study therapy are shown in Supplementary Table 3. External validity was evaluated in 2945 eligible patients from the Swedish Multiple Sclerosis Registry.

Predictors of treatment response

In this exploratory step, all baseline demographic, clinical and paraclinical patient characteristics (Table 2) were evaluated for their associations with the defined on-treatment disease outcomes (cumulative probability of disability progression or regression, multiple sclerosis relapses, conversion to secondary progressive disease, ΔAUC, or probability of treatment discontinuation) in a series of univariate models. A large number of associations were identified. As an example, the variables associated with the probability of disability progression events for each of the studied DMTs are shown in Table 2. A number of associations were consistent between DMTs, such as, a greater risk of disability progression in older age, secondary progressive multiple sclerosis, more severe disability, more pronounced impairment of gait, or history of relapses with incomplete recovery. These variables can therefore be considered as prognostic markers of disease outcomes. Several other variables showed differential associations with disability progression hazard across DMTs (in terms of both the strength and the direction), such as the most recent DMT. These variables therefore acted as modifiers of treatment effect (Sormani, 2017). The above exploratory analyses were unadjusted for the numerous confounders inherent in the observational data and therefore are not to be interpreted as independent predictive markers.

Principal components

To evaluate independent predictors of disease outcomes without the risk of model overparametrization,

Table 1 Characteristics of the study population at the start of the study therapy

Source	Training cohort MSBase	Testing cohort MSBase	Validation cohort Swedish Multiple Sclerosis Registry
Patients (% female)	8513 (72)	1196 (73)	2945 (72)
Age, years[a]	37.9 ± 10.2	37.2 ± 10.0	39.1 ± 10.8
Disease duration, years[b]	6.6 (2.5, 12.4)	7.0 (1.8, 12.2)	6.6 (2.4, 12.3)
Disease course, patients			
Clinically isolated syndrome (%)	609 (7)	90 (8)	n/a
Relapsing-remitting (%)	7167 (84)	1014 (85)	2886 (98)
Secondary progressive (%)	634 (7)	86 (7)	n/a
Active primary progressive (%)	103 (1)	6 (0.5)	59 (2)
Disability, EDSS step[b]	2.5 (1.5, 4)	2.5 (1.5, 4)	2.5 (1.5, 3.5)
Functional system score: pyramidal[b]	1 (1, 3)	2 (1, 3)	n/a
Functional system score: sensory[b]	1 (0, 2)	1 (0, 2)	n/a
Functional system score: visual[b]	0 (0, 1)	0 (0, 1)	n/a
Functional system score: cerebellar[b]	0 (0, 2)	0 (0, 2)	n/a
Functional system score: brainstem[b]	0 (0, 1)	0 (0, 1)	n/a
Functional system score: sphincteric[b]	0 (0, 1)	0 (0, 1)	n/a
Functional system score: cerebral[b]	0 (0, 0)	0 (0, 0)	n/a
Functional system score: ambulatory[b]	0 (0, 0)	0 (0, 0)	n/a
EDSS trajectory, slope[b]	+0.3 (0.1, 0.7)	+0.3 (0.1, 0.6)	+0.3 (0.1, 0.8)
EDSS change in the previous year			
Increase, patients (%)	1847 (22)	245 (21)	615 (21)
Decrease, patients (%)	627 (7)	95 (8)	177 (6)
Total number of previous relapses[b]	3 (2, 6)	4 (2, 6)	2 (1, 3)
Annualized relapse rate[b]	1.1 (0.7, 2.0)	1.1 (0.7, 2.0)	0.95 (0.4, 1.7)
Prior on-treatment relapses[b]	0 (0, 2)	0 (0, 2)	0 (0, 1)
Relapses in the preceding ear[b]	1 (0, 2)	1 (0, 2)	1 (0, 2)
Predominant relapse phenotype			
Pyramidal (%)	2161 (25)	317 (27)	n/a
Sensory (%)	2515 (30)	372 (31)	n/a
Visual (%)	1073 (13)	135 (11)	n/a
Brainstem (%)	862 (10)	130 (11)	n/a
Cerebellar (%)	353 (4)	44 (4)	n/a
Sphincteric (%)	94 (1)	5 (0.4)	n/a
Cerebral (%)	22 (0.3)	4 (0.3)	n/a
Brain MRI			
Active (%)	1491 (18)	197 (17)	591 (20)
Missing (%)	4347 (51)	612 (51)	1278 (43)
Spinal MRI			
Active (%)	427 (6)	48 (4)	66 (2)
Missing (%)	7609 (89)	1074 (90)	2768 (94)
Follow-up duration, years[a]	9.0 ± 5.1	9.4 ± 5.2	9.4 ± 4.8
Number of on-study visits[b]	8 (4, 14)	9 (5, 15)	7 (4, 10)
Treatment persistence, years[b]	2.3 (1.3, 4.2)	2.3 (1.2, 4.0)	3 (1.5, 5.1)
Number of previous DMTs[b]	1 (0, 1)	1 (0, 2)	1 (0, 2)
Time from discontinuing previous DMT, years[b]	0 (0, 0.1)	0 (0, 0.1)	0 (0, 0.1)
On-study DMT, patients			
Interferon β-1a, IM	1720	191	678
Interferon β-1a, SC	2660	295	265
Interferon β-1b	1317	146	242
Glatiramer acetate	1792	199	523
Fingolimod	1483	164	530
Natalizumab	1431	159	1231
Mitoxantrone	404	44	217

[a]Mean ± standard deviation.
[b]Median (quartiles).
IM = intramuscular; n/a = data not available; SC = subcutaneous.

Table 2 Predictors of disability progression events for each of the analysed therapies

	Interferon β − 1a, IM	Interferon β − 1a, SC	Interferon β − 1b	Glatiramer acetate	Fingolimod	Natalizumab	Mitoxantrone
Demographic and general clinical information							
Sex							
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	–	–	–	np	–	0.35 ± 0.15	–
Age	0.03 ± 0.01	−0.04 ± 0.01	0.03 ± 0.00	0.02 ± 0.01	n/a	0.03 ± 0.01	–
Disease duration	np	−0.07 ± 0.02	0.03 ± 0.01	0.03 ± 0.01	–	–	–
Disease course							
Relapsing-remitting	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Clinically isolated syndrome	−0.54 ± 0.17	–	−0.51 ± 0.26	–	–	−14.00 ± 0.43	−14.57 ± 0.53
Secondary progressive	0.61 ± 0.24	–	0.76 ± 0.12	0.72 ± 0.18	1.16 ± 0.19	0.67 ± 0.27	1.03 ± 0.30
Progressive-relapsing	–	–	0.86 ± 0.33	0.92 ± 0.31	–	–	–
First symptom:							
Supratentorial	–	–	–	–	–	–	–
Optic pathways	–	–	–	–	–	–	–
Brainstem	–	–	–	–	−0.39 ± 0.2	–	–
Spinal cord	–	0.45 ± 0.17	–	–	–	–	−1.14 ± 0.46
Disability							
Disability, EDSS	np	0.38 ± 0.04	0.14 ± 0.03	0.15 ± 0.03	0.10 ± 0.04	–	–
EDSS trajectory, slope	−0.18 ± 0.04	0.28 ± 0.03	−0.14 ± 0.05	−0.15 ± 0.06	–	–	–
EDSS change							
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Increase	0.49 ± 0.16	−1.37 ± 0.59	–	–	0.85 ± 0.23	0.87 ± 0.25	–
Decrease	–	1.08 ± 0.15	np	–	−0.42 ± 0.22	–	–
EDSS functional system score:							
Pyramidal	0.14 ± 0.06	0.17 ± 0.07	0.23 ± 0.04	np	0.14 ± 0.07	–	–
Sensory	–	0.35 ± 0.08	–	–	–	−0.19 ± 0.07	–
Visual	−0.22 ± 0.09	–	–	–	–	–	–
Brainstem	0.18 ± 0.08	–	–	0.25 ± 0.06	–	–	–
Cerebellar	np	0.29 ± 0.08	0.18 ± 0.05	0.29 ± 0.05	0.24 ± 0.07	0.17 ± 0.06	–
Sphincteric	np	–	0.26 ± 0.06	–	–	0.15 ± 0.07	–
Cerebral	–	–	–	–	–	–	–
Ambulatory	–	0.21 ± 0.05	0.09 ± 0.03	0.09 ± 0.03	0.12 ± 0.04	0.06 ± 0.03	0.11 ± 0.05
Therapy							
Previous DMTs, number	0.11 ± 0.06	−0.35 ± 0.13	–	0.15 ± 0.04	–	–	–
Time from the previous DMT	$-4 \times 10^{-4} \pm 10^{-4}$	–	–	$4x10^{-4} \pm 10^{-4}$	–	–	–
Most recent prior DMT							
None							
Stem cell therapy	n/a	n/a	n/a	1.47 ± 0.70	n/a	n/a	n/a
Interferon β-1a, IM	–	−0.56 ± 0.21	–	0.47 ± 0.17	–	np	–
Interferon β-1a, SC	–	−0.53 ± 0.21	–	0.39 ± 0.15	–	–	–
Interferon β-1b	np	−1.73 ± 0.72	−0.37 ± 0.18	0.50 ± 0.17	–	–	–
Glatiramer acetate	–	–	0.44 ± 0.19	–	–	–	–
Teriflunomide	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Dimethyl fumarate	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Fingolimod	–	–	–	n/a	–	0.83 ± 0.43	1.49 ± 0.59
Cladribine	n/a	n/a	n/a	n/a	–	–	n/a
Natalizumab	–	–	–	0.96 ± 0.34	–	–	–
Alemtuzumab	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Rituximab	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mitoxantrone	–	–	–	–	–	–	–
Most active prior DMT							
None							
Interferon β-1a, IM	–	−0.43 ± 0.21	–	–	–	–	–
Interferon β-1a, SC	–	−0.49 ± 0.21	–	–	–	−0.57 ± 0.19	−0.78 ± 0.35
Interferon β-1b	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Glatiramer acetate	–	–	–	–	–	–	–
Teriflunomide	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Dimethyl fumarate	n/a	n/a	n/a	–	n/a	–	n/a
Fingolimod	1.7 ± 0.88	–	n/a	n/a	n/a	–	n/a

(continued)

Table 2 Continued

	Interferon β – 1a, IM	Interferon β – 1a, SC	Interferon β – 1b	Glatiramer acetate	Fingolimod	Natalizumab	Mitoxantrone
Cladribine	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Natalizumab	n/a	–	–	1.06 ± 0.33	–	–	–
Alemtuzumab	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mitoxantrone	–	–	–	–	–	–	–
Disease activity							
Annualized relapse rate	0.10 ± 0.03	np	–	0.09 ± 0.02	–	–	–
Relapses in the previous year	–	0.42 ± 0.06	–	–	−0.33 ± 0.10	−0.35 ± 0.08	−0.23 ± 0.11
Relapses with impact on activities of daily living	–	0.19 ± 0.06	–	–	–	–	–
Relapses with impact on activities of daily living (last 2 years)	–	0.51 ± 0.12	−0.46 ± 0.20	–	–	–	–
Severe relapses	–	–	–	–	–	–	–
Severe relapses (last 2 years)	−0.28 ± 0.13	0.25 ± 0.09	–	–	–	–	–
Relapses with poor recovery	0.20 ± 0.05	0.16 ± 0.04	np	0.14 ± 0.03	0.10 ± 0.04	–	–
Relapses with poor recovery (last 2 years)	0.21 ± 0.10	0.46 ± 0.09	–	0.23 ± 0.08	–	–	–
Relapses on DMTs	0.12 ± 0.03	–	–	0.05 ± 0.02	−0.06 ± 0.03	–	−0.14 ± 0.06
Predominant relapse phenotype							
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Pyramidal	–	–	–	–	–	–	–
Sensory	np	–	−0.45 ± 0.16	−0.37 ± 0.16	−0.71 ± 0.23	−0.82 ± 0.25	−0.88 ± 0.41
Visual	−0.41 ± 0.19	–	−0.50 ± 0.20	−0.91 ± 0.25	−0.74 ± 0.33	−0.88 ± 0.40	–
Brainstem	−0.41 ± 0.20	−0.87 ± 0.35	−0.66 ± 0.22	−0.53 ± 0.23	−0.93 ± 0.4	–	–
Cerebellar	–	–	–	–	–	–	–
Sphincteric	0.89 ± 0.34	–	–	–	np	n/a	n/a
Cerebral	–	n/a	n/a	–	n/a	–	n/a
Relapses in the last 2 years							
Pyramidal	0.27 ± 0.08	0.21 ± 0.08	–	0.19 ± 0.07	–	–	–
Sensory	–	0.23 ± 0.06	–	np	−0.47 ± 0.14	−0.39 ± 0.09	−0.51 ± 0.24
Visual	–	–	−0.63 ± 0.17	–	−0.70 ± 0.29	–	–
Brainstem	–	–	−0.39 ± 0.12	–	–	–	–
Cerebellar	–	0.46 ± 0.16	–	0.38 ± 0.11	−1.03 ± 0.38	–	–
Sphincteric	0.45 ± 0.14	–	–	0.51 ± 0.16	–	–	–
Cerebral	–	–	–	–	n/a	–	–
Brain MRI							
Active	–	0.61 ± 0.20	−0.66 ± 0.22	–	–	–	–
Inactive	–	–	–	–	–	–	–
Spinal MRI							
Active	–	0.62 ± 0.27	–	–	–	–	–
Inactive	–	0.66 ± 0.30	–	–	–	–	–
CSF							
Abnormal, multiple sclerosis-typical	–	–	–	np	–	–	–
Abnormal, multiple sclerosis -atypical	–	–	–	–	np	–	–

The table shows the β coefficients ± standard error for univariate Andersen-Gill regression models. Only the coefficients that reached the level of statistical significance $\alpha \leq 0.05$ are shown. IM = intramuscular; n/a = insufficient data/poor model fit; np = violation of the proportionality of hazards assumption; Ref = Reference value; SC = subcutaneous.

dimensionality of the multivariable models was first reduced by principal component analysis. Three principal components (PC1–3) were identified, with the eigenvalues of 0.0019, 0.0013 and 0.0010, and with the proportion of explained variance of 13%, 9% and 7%, respectively. The loadings of the variables into the three components are shown in Table 3. PC1 is representative primarily of the overall neurological disability, its components, the previous therapy and the previous treatment response. PC2 represents mainly the frequency, severity and impact of the previous multiple sclerosis relapses, patient age and multiple sclerosis course. PC3 represents mainly the first multiple sclerosis presentation. Categorized outcomes of brain and spinal MRI scans contributed small loadings to all three

Table 3 Variable loadings into the three principal components

Principal component	PC 1	PC 2	PC 3
Demographic and general clinical information			
Sex	−0.003	−0.009	−0.002
Age	0.044	**−0.058**	0.002
Disease duration	0.019	−0.026	0.016
Disease course	0.066	**−0.057**	−0.006
First symptom: supratentorial (y/n)	0.003	0.043	**0.123**
First symptom: optic pathways (y/n)	0.002	0.039	**0.115**
First symptom: brainstem (y/n)	0.002	0.041	**0.122**
First symptom: spinal cord (y/n)	0.005	0.042	**0.120**
Disability			
Disability, EDSS	**0.121**	−0.054	−0.014
EDSS trajectory, slope	−0.030	0.049	−0.032
EDSS change (increase/decrease)	0.046	0.001	−0.004
EDSS functional system score:			
Pyramidal	**0.101**	−0.048	−0.005
Sensory	0.071	−0.018	0.001
Visual	0.033	−0.015	−0.015
Brainstem	0.052	−0.031	−0.011
Cerebellar	**0.088**	−0.041	−0.010
Sphincteric	**0.086**	−0.043	−0.007
Cerebral	0.056	−0.032	−0.016
Ambulatory	**0.101**	−0.051	−0.012
Therapy			
Previous DMTs, number	**0.087**	−0.032	0.041
Time from the previous DMT	0.052	−0.030	0.027
Most recent prior DMT	**0.088**	−0.047	0.049
Most active prior DMT	0.066	−0.032	0.043
Disease activity			
Annualized relapse rate	0.024	**0.068**	−0.019
Relapses in the previous year	0.033	**0.108**	−0.030
Relapses with impact on activities of daily living	0.065	0.043	−0.013
Relapses with impact on activities of daily living (last 2 years)	0.058	**0.073**	−0.029
Severe relapses	0.081	**0.054**	0.003
Severe relapses (last 2 years)	0.072	**0.090**	−0.019
Relapses with poor recovery	**0.086**	0.040	−0.009
Relapses with poor recovery (last 2 years)	0.070	**0.074**	−0.029
Relapses on DMTs	**0.085**	0.010	0.028
Predominant relapse phenotype	0.050	0.034	0.034
Relapses in the last 2 years			
Pyramidal	0.076	**0.070**	−0.016
Sensory	0.028	**0.087**	−0.006
Visual	−0.002	0.050	−0.021
Brainstem	0.013	0.052	−0.018
Cerebellar	0.048	0.039	−0.028
Sphincteric	0.032	0.037	−0.020
Cerebral	0.020	0.017	−0.021
Brain MRI	0.018	−0.002	−0.011
Brain MRI activity	−0.004	−0.023	−0.006
Spinal MRI	0.020	0.009	0.016
Spinal MRI activity	−0.011	−0.017	−0.009
CSF	0.004	−0.011	−0.014

The table shows loadings of the variables included in the non-linear principal component analysis into the three principal components. The variables with the largest loadings into each of the principal components are shown in bold.

Table 4 Associations between the principal components and treatment outcomes for each of the analysed therapies

	Interferon β-1a, IM	Interferon β-1a, SC	Interferon β-1b	Glatiramer acetate	Fingolimod	Natalizumab	Mitoxantrone
Disability progression events							
PC 1	29 ± 9	23 ± 7	14 ± 7	31 ± 6	–	–	–
PC 2	–	−31 ± 9	−36 ± 10	–	−48 ± 16	−39 ± 15	−41 ± 17
PC 3	48 ± 18	–	–	–	–	–	–
Disability regression events							
PC 1	38 ± 12	49 ± 9	42 ± 9	30 ± 9	34 ± 8	34 ± 8	–
PC 2	–	45 ± 10	50 ± 11	–	33 ± 10	–	69 ± 18
PC 3	−57 ± 12	−43 ± 10	−27 ± 12	–	–	–	–
Incidence of relapses							
PC 1	28 ± 4	23 ± 3	–	25 ± 4	28 ± 4	32 ± 5	–
PC 2	44 ± 6	38 ± 4	41 ± 5	39 ± 6	20 ± 6	20 ± 7	43 ± 12
PC 3	–	–	−19 ± 7	–	–	38 ± 19	–
Conversion to secondary progressive multiple sclerosis							
PC 1	109 ± 15	93 ± 10	58 ± 11	79 ± 11	78 ± 13	52 ± 12	57 ± 22
PC 2	−69 ± 22	−60 ± 14	−67 ± 16	−35 ± 16	−64 ± 19	−84 ± 16	−81 ± 27
PC 3	–	–	–	–	–	–	–
Annualized change in the area under disability–time curve							
PC 1	−15 ± 3	−14 ± 2	−13 ± 3	−9 ± 2	−13 ± 2	−15 ± 3	–
PC 2	–	−13 ± 3	−17 ± 4	−8 ± 4	−10 ± 3	−11 ± 4	−13 ± 4
PC 3	17 ± 4	16 ± 3	9 ± 4	–	–	17 ± 8	–
Discontinuation of therapy							
PC 1	39 ± 5	17 ± 3	17 ± 4	16 ± 4	24 ± 7	–	–
PC 2	–	–	11 ± 5	–	–	–	–
PC 3	–	–	–	–	64 ± 32	–	–

The table shows β coefficients for multivariable Andersen-Gill, Cox or linear regression models (as appropriate for the distribution of the outcome variables, see the 'Materials and methods' section). Only the coefficients that reached the level of statistical significance $\alpha \leq 0.05$ are shown.
IM = intramuscular; n/a = insufficient data; PC = principal component; SC = subcutaneous.

principal components. Distribution of the principal components in the training cohort is shown in Supplementary Fig. 3. The estimated principal components and the principal components reconstructed using the individual patient characteristics and their loadings were highly correlated (Supplementary Fig. 4). In addition, two adjustment components were calculated as described above.

Multivariable predictive models

The independent associations between the principal components and the probability of the defined multiple sclerosis outcomes for each DMT and treatment outcome are shown in Table 4. Several consistent patterns were identified across the treatment groups. PC1 (representing mainly disability and previous therapy) was positively associated with disability progression, regression, relapse incidence, secondary progressive multiple sclerosis and DMT discontinuation, and negatively associated with ΔAUC for interferon β and glatiramer acetate. It was also associated with some of the above outcomes for fingolimod and natalizumab. PC2 (representing mainly the relapse-related variables) was positively associated with on-treatment relapse incidence and regression events (across all DMTs), and negatively associated with progression events, secondary progressive multiple sclerosis and ΔAUC mainly for interferon β and glatiramer acetate, but partly also for fingolimod, natalizumab, and mitoxantrone. PC3 (representing mainly the multiple sclerosis onset phenotype) was positively associated with ΔAUC, and negatively associated with disability regression events mainly for interferon β. Importantly, associations specific for the different DMTs were observed (Table 4), indicating that the models did not merely predict overall disease outcomes but estimated DMT-specific outcomes.

Individual prediction of multiple sclerosis outcomes

The coefficients presented in Table 4 and their margins or error formed the basis for the 42 predictive models (Supplementary Table 4). Figures 1 and 2 show two examples of prediction of treatment outcomes for interferon β-1a subcutaneous and natalizumab. The figures show the most likely number of events experienced by a patient treated with either DMT over up to 4 years, or the predicted area under disability-time curve. The first patient, with moderately advanced, active relapsing-remitting multiple sclerosis, is likely to derive a relatively greater benefit from natalizumab—in terms of minimising relapse frequency, progression of disability and, notably, the risk of

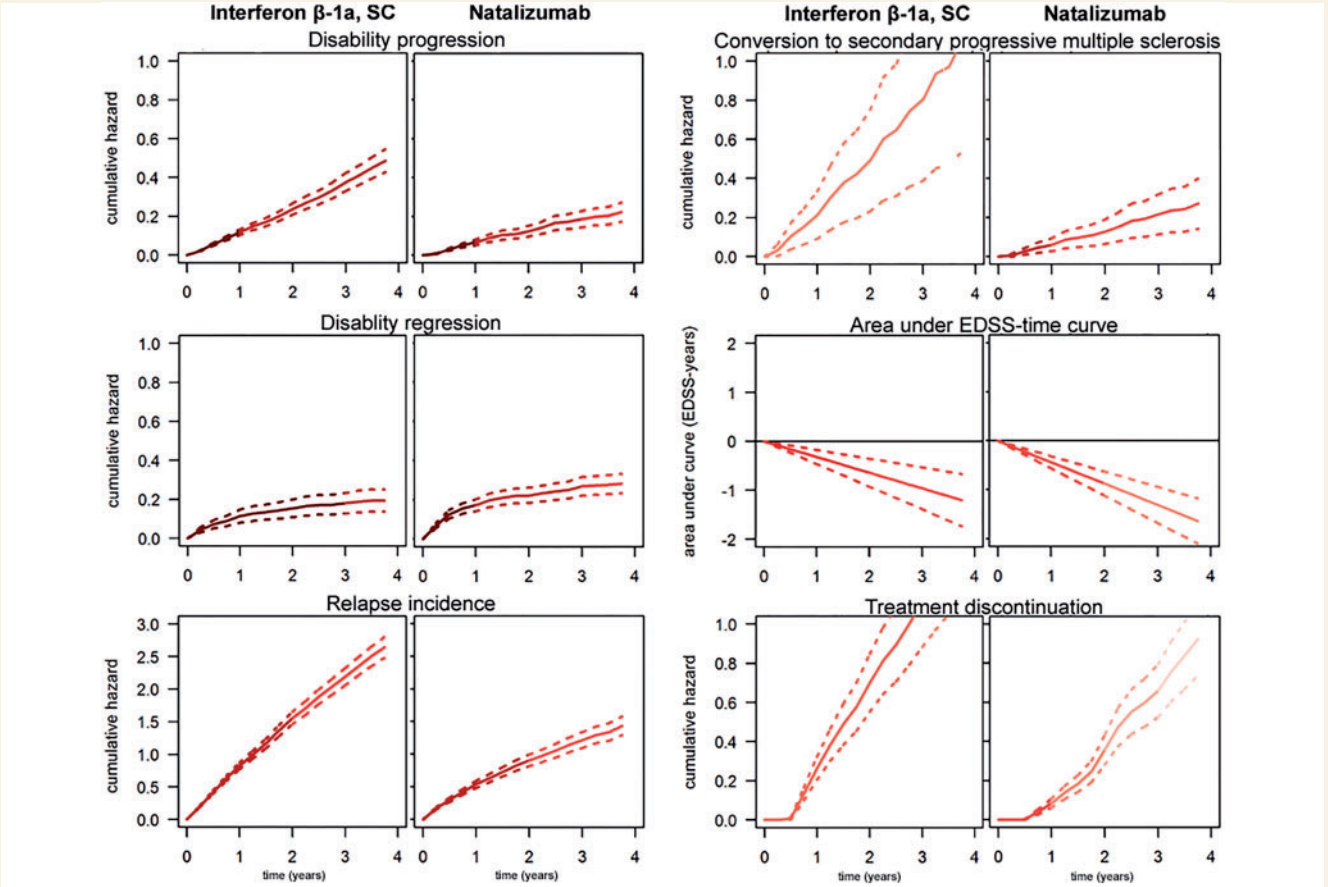

Figure 1 An example of individual prediction of response to interferon β-1a and natalizumab in moderately advanced, active multiple sclerosis. Six treatment outcomes are predicted for a 43-year-old female with relapsing-remitting multiple sclerosis, with an EDSS score of 5 (with sensory functional score of 4, and pyramidal, cerebellar and ambulatory functional scores of 3) and increase in the EDSS score within the previous year, who first presented with spinal cord symptoms at the age of 33. The patient had previously experienced 10 multiple sclerosis relapses, mostly with pyramidal symptoms, six of these of high severity and one while treated with DMTs, with the most recent relapse having occurred 51 days before the date of the prediction. She was previously treated with two DMTs, her most aggressive DMT was natalizumab and she discontinued interferon β-1a subcutaneous 51 days before the prediction. Her brain and spinal cord MRI showed abnormal findings in keeping with the diagnosis of multiple sclerosis and her CSF showed oligoclonal bands that were not present in the serum. Information about 74–93% of the variables informing the predictive models was available. The curves represent the most probable number of outcome events or area under EDSS-time curve (±95% prediction interval) over the next 4 years if recommencing natalizumab or interferon β-1a subcutaneous. The shading of the curves illustrates the robustness of the prediction (quantified as the product of the size of the training cohort and the accuracy of the prediction in the testing cohort).

conversion to secondary progressive multiple sclerosis. In contrast, the second patient, who is treatment-naïve and at the early stage of her disease, is likely to experience similar disability outcomes on either therapy, only with a relatively greater suppression of relapse frequency by natalizumab. Supplementary Fig. 5 illustrates the effect of data missingness on the predictive models. When only patient sex, age, disease duration and the number of previous relapses is considered, the ability of the models to differentiate between the two therapeutic approaches diminishes—in particular, it affects the prediction of conversion to secondary progressive disease and ΔAUC. Figure 3 presents an example of a full prediction of disability progression events for the seven DMTs in a patient with active secondary progressive multiple sclerosis, for whom the hazard of disability progression events is likely to be better mitigated by high-efficacy DMTs compared with injectable platform therapies (Lizak *et al.*, 2017). An example of a full prediction of all six treatment outcomes in seven DMTs is given in Supplementary Fig. 6.

Prediction accuracy and validity

Accuracy of the predictive models in the training cohorts is shown in Supplementary Table 5 and their validity in the testing cohorts is shown in Supplementary Fig. 7. The accuracy and internal validity of the predictive models was high for disability progression, disability regression and relapse incidence during the first year, moderate for relapse incidence for Years 2–4 and ΔAUC, and low for conversion to secondary progressive multiple sclerosis and treatment discontinuation.

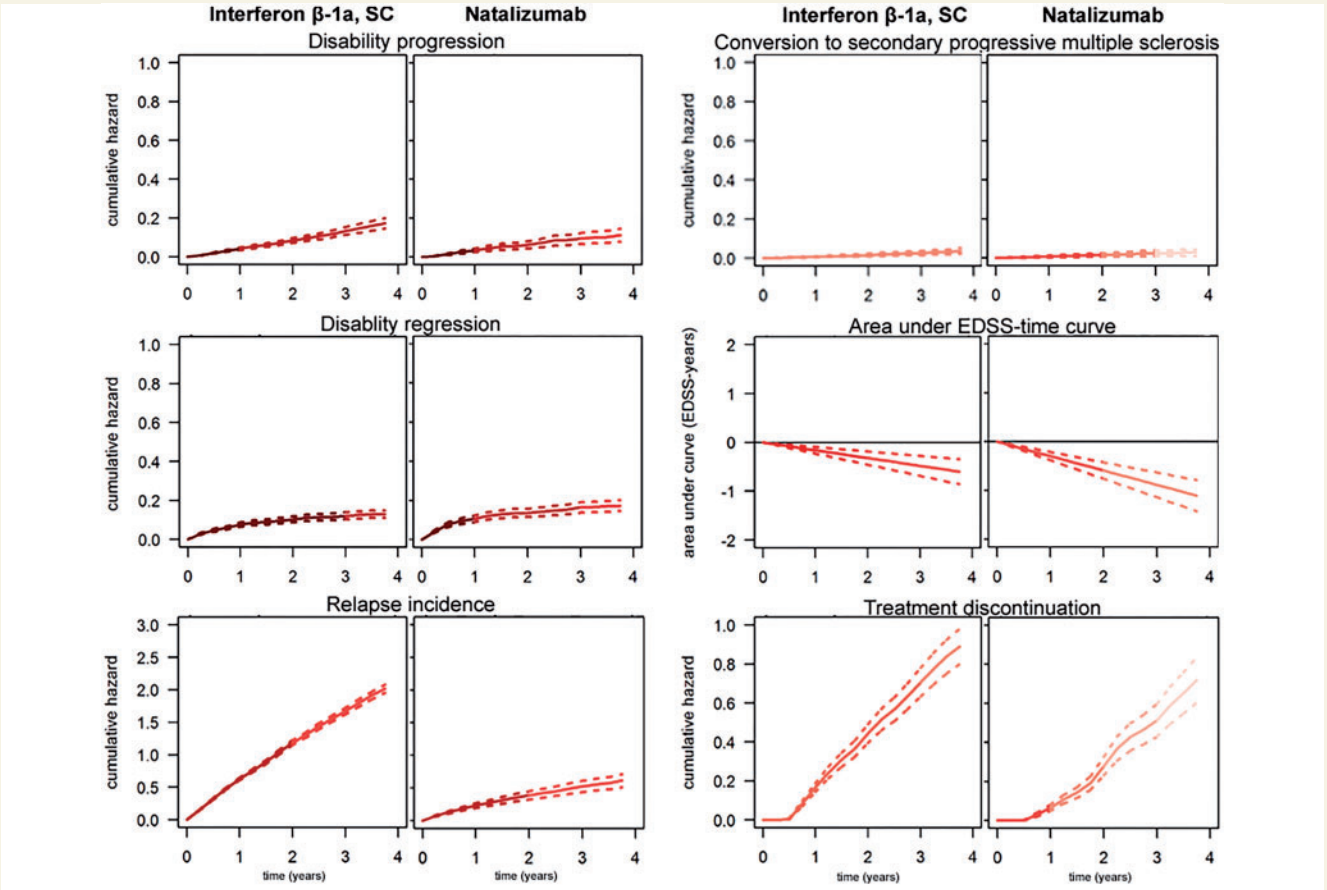

Figure 2 An example of individual prediction of response to interferon beta-1a and natalizumab in early multiple sclerosis. Six treatment outcomes are predicted for a 35-year-old female with relapsing-remitting multiple sclerosis, with an EDSS score of 2.5 (sensory and cerebellar functional system scores of 2 and cerebral functional system score of 1) and a mean increase in EDSS by 2.5 steps during the previous 6 months, who presented with the first multiple sclerosis symptoms less than a year ago. The patient has experienced two relapses, both with incomplete recovery, the most recent relapse recorded 15 days prior to the prediction date. She was not previously treated. Her brain and spinal cord MRI showed abnormal findings in keeping with the diagnosis of multiple sclerosis and her CSF showed oligoclonal bands that were not present in the serum. Information regarding 74–93% of the variables informing the predictive models was available. The curves represent the most probable number of outcome events or area under EDSS-time curve (±95% prediction interval) over the next 4 years if switching to natalizumab or interferon β-1a subcutaneous. The shading of the curves illustrates the robustness of the prediction (quantified as the product of the size of the training cohort and accuracy of the prediction in the testing cohort).

Table 5 shows the results of the evaluation of external validity of the predictive models in an independent database (Swedish Multiple Sclerosis Registry). Between 217 and 1231 eligible patients were identified for the studied therapies. Similar to the results of accuracy and internal validity, the overall 4-year prediction was highly accurate for disability progression, disability regression and relapse incidence. The external validity was moderate for the prediction of ΔAUC and low for the prediction of conversion to secondary progressive disease and treatment discontinuation.

Discussion

Using MSBase, a large global cohort study, and Swedish Multiple Sclerosis Registry, a population-based national registry, we have designed and validated comprehensive predictive models of the outcomes of treatment with seven commonly used disease modifying therapies for multiple sclerosis.

Modifiers of treatment outcomes

The multivariable models confirmed our hypothesis that treatment outcomes vary with respect to patients' demographic and clinical characteristics. Moreover, we have observed that the associations between these demographic and clinical treatment effect modifiers and the treatment outcomes vary among DMTs, an observation that is the key to individualized therapy (Sormani, 2017). For example, the higher probability of disability progression during treatment with interferon β or glatiramer acetate was predominantly associated with a greater disability at the treatment commencement and high severity and poor

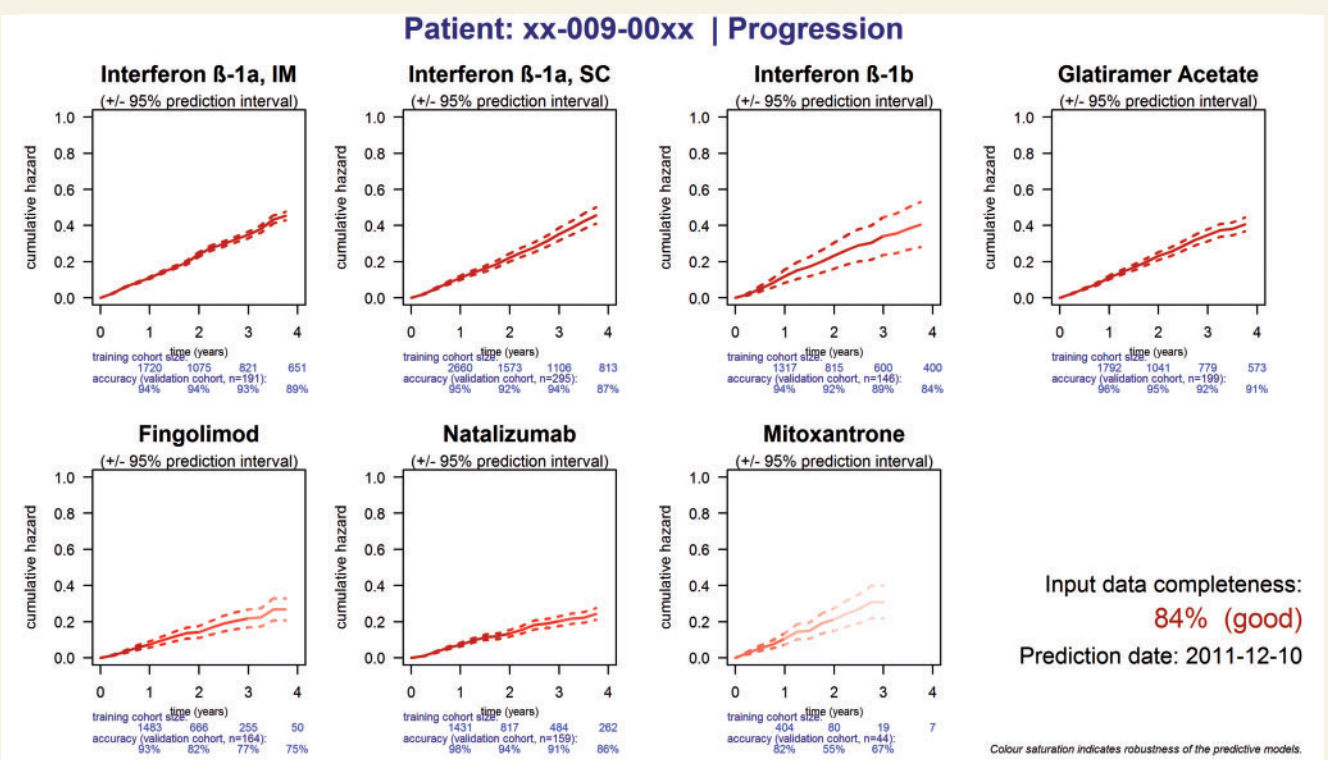

Figure 3 An output of the models predicting 6-month confirmed disability progression for seven DMTs in a 43-year-old male with highly active secondary progressive multiple sclerosis. He experienced nine multiple sclerosis relapses since disease onset 10 years prior to the prediction, predominantly with pyramidal symptomatology, including a relapse 29 days prior to the prediction date. Five relapses were recorded as severe, with seven occurring while treated with DMTs. Four relapses were followed by incomplete recovery and the current EDSS step was 5. Until 11 days prior to the prediction, he was treated with interferon β-1a subcutaneously. Brain MRI showed findings typical for multiple sclerosis. The curves represent the most probable number of confirmed disability progression events (±95% prediction interval) over the next 4 years. The shading of the curves illustrates the robustness of the prediction (quantified as the product of the size of the training cohort and accuracy of the prediction in the testing cohort).

Table 5 External validity of the predictive algorithm

DMT	External validation cohort	Relapses, %	Disability progression, %	Disability regression, %	Annualized change in AUC, %	Secondary progressive disease, %	Discontinuation, %
Interferon β-1a, IM	678	79	93	96	39	19	9
Interferon β-1a, SC	265	83	91	96	31	42	10
Interferon β-1b	242	82	89	94	41	19	5
Glatiramer acetate	523	79	92	96	40	9	9
Fingolimod	530	92	96	95	39	33	13
Natalizumab	1231	95	95	86	47	18	3
Mitoxantrone	217	94	86	95	34	7	6

Proportion of the eligible patients from the Swedish National Multiple Sclerosis Cohort in whom the predictive outcomes over 4 years after commencing index therapy fulfilled the definition of accurate prediction. IM = intramuscular; SC = subcutaneous.

recovery from prior relapses. During treatment with fingolimod, natalizumab or mitoxantrone, higher risk of disability progression was mainly associated with lower relapse activity within the year prior to commencing therapy. The probability of disability regression was predominantly associated with pre-baseline disability, therapy and high relapse activity. As expected, incidence of relapses was associated with pretreatment relapse activity, younger age and relapsing-remitting disease course for all therapies, however, the strength of these associations varied among DMTs. Similarly, conversion to secondary progressive disease showed variable associations with higher disability scores

and lower relapse activity. Increase in the overall disability burden was associated with lower pretreatment disability and relapse activity, less aggressive therapy, younger age and relapsing-remitting disease course. The associations for the discontinuation of therapy were highly variable among DMTs.

Previous studies have evaluated modifiers of composite treatment outcomes, defined as 'treatment response'. The definitions typically consisted of combinations of relapse activity, its reduction, relapse severity, disability accrual and radiological activity (Trojano *et al.*, 2003; Waubant *et al.*, 2003; Portaccio *et al.*, 2006; Horakova *et al.*, 2012; Prosperini *et al.*, 2012; Sargento Freitas *et al.*, 2013). These studies identified indicators of poor response to interferon β as younger age at treatment start (Waubant *et al.*, 2003) or disease onset (Fromont *et al.*, 2008), shorter (Waubant *et al.*, 2003) or longer (Trojano *et al.*, 2003) disease duration, low (Trojano *et al.*, 2003; Waubant *et al.*, 2003; Portaccio *et al.*, 2006; Fromont *et al.*, 2008) or high (Coppola *et al.*, 2006; Portaccio *et al.*, 2006; Sellebjerg *et al.*, 2014) pretreatment relapse activity, greater disability (Coppola *et al.*, 2006; O'Rourke *et al.*, 2007), and monosymptomatic multiple sclerosis onset (Fromont *et al.*, 2008). In addition, two studies identified lower (Sargento Freitas *et al.*, 2013) or higher (Prosperini *et al.*, 2012) relapse activity, and higher disability (Prosperini *et al.*, 2012) as indicators of poor response to natalizumab over 2 years. The variability among the published studies is most likely attributable to the variability in the definition of treatment response and study populations. Our present study confirms a number of the above observations and provides a comprehensive prediction of individual treatment outcome metrics rather than a composite prediction of overall treatment response. The individual outcome metrics are of a greater relevance to neurologists than composite classifiers (such as the presence or absence of treatment failure) as they facilitate more granular discussion, beyond the broad terms of the 'poor versus good' response dichotomy.

Numerous other molecular, genetic and quantitative radiological modifiers of treatment outcomes have been proposed (Bosca *et al.*, 2010; Vosslamber *et al.*, 2011; Horakova *et al.*, 2012; Malhotra *et al.*, 2013; Mahurkar *et al.*, 2014; Matas *et al.*, 2014; Uher *et al.*, 2014; Charbit *et al.*, 2015; Hegen *et al.*, 2016; Kuhle *et al.*, 2017). While these modifiers could add significantly to the predictive models by incorporating pathophysiological mechanisms of on-treatment multiple sclerosis activity, their availability in clinical practice is at the present time limited, as many are still awaiting validation.

Analytical approach

Observational data are subject to multiple biases, including indication and detection bias, and Will Rogers phenomenon (Kalincik and Butzkueven, 2016). Relative to comparative studies of treatment outcomes, the impact of these biases on the modifiers of treatment outcomes in a non-comparative setting is less pronounced. To ameliorate the bias, all multivariable models were adjusted for a large number of potential confounders, including sex, age, disease duration, disability, previous disease activity and MRI (indication bias), centre, visit frequency, and the number of EDSS scores (detection bias), and the date of treatment start (Will Rogers phenomenon). We have shown that, at least in some situations, reduced information limits the ability of the models to differentiate between outcomes of different treatment strategies. Therefore, access to comprehensive information about patients and their disease is a key to robust prognostics.

To prevent overparametrization, whose risk would be high in the inclusive multivariable models, we have reduced dimensionality of the models using principal component analysis. While this approach has resulted in good model fit and better control of missing data, it precludes detailed evaluation of the independent associations between the treatment modifiers and treatment response. Instead, the models are based on cumulative information represented in the three principal components, which mirror the known epidemiology and pathophysiology of multiple sclerosis: (i) patients' disability and previous exposure and response to DMTs; (ii) history of relapses (including their frequency, severity and recovery), age, disease phenotype; and (iii) the initial multiple sclerosis symptoms.

In addition, the models included cohort-specific adjustment in order to mitigate the effects of the geography- and site-specific variability, and flux in diagnostic and management strategies. This adjustment was used in the study models but not in the implemented predictive models, as outside the training cohort it would introduce extrapolation beyond the available data.

Accuracy of the predictive models

We have addressed the issue of internal validity by evaluating the accuracy of the predictive models in validation cohorts that were separate from the training cohorts. The observed accuracy and validity were satisfactory, in particular for the 4-year prediction of disability progression and regression and 1-year incidence of relapses. Importantly, evaluation of external validity in a geographically non-overlapping cohort (Swedish Multiple Sclerosis Registry) showed prediction accuracy that was very similar to the results of internal validation from the MSBase cohort. This result represents an independent replication of the primary analyses and demonstrates broad generalizability of its results.

The criteria for evaluating the internal and external validity of the predictive models were focused on point predictors. This is a conservative approach, as in addition to the mean predicted event incidence, clinicians are also provided with the indication of uncertainty of each prediction in the form of the 95% prediction intervals. This facilitates a realistic interpretation of the predicted mean values in the context of their accuracy and robustness (Fig. 3).

Limitations

It should be noted that for some DMTs, such as cladribine, alemtuzumab, teriflunomide or dimethyl fumarate, the available treated cohorts were either too small or the recorded follow-up was too short to enable development of informative predictive models. These models will be included in the future iterations of the predictive algorithm.

Data missingness for brain and spinal MRI was high. Furthermore, the classification of MRI activity was binary (present/absent). Finally, the MRI data were physician-reported and therefore subject to inter-scanner and inter-rater error. These factors may lead to underestimation of the true predictive value of these variables in relation to the treatment outcomes. The fact that the predictive analysis is based entirely on demographic, clinical and paraclinical information precludes evaluation of any underlying pathophysiological mechanisms of treatment response. These will be enabled by future inclusion of molecular or genetic markers in the existing models. For example, the risk of adverse events could not be predicted based on the available information (data not shown). On the other hand, like the models predicting conversion to definite multiple sclerosis (Tintore *et al.*, 2015; Spelman *et al.*, 2016), our models of individual treatment response use commonly accessible information and are therefore readily applicable in clinical practice.

Conclusion

The Multiple Sclerosis Brain Health initiative has highlighted the importance of 'treating the right patient with the right drug at the right time' in order to prevent accumulation of irreversible neurological and cognitive disability and maximize outcomes in patients with multiple sclerosis (www.msbrainhealth.org; accessed on 30/08/2016). Our present study identifies patterns in the prevalent multiple sclerosis population, whose predictive value exceeds that of the isolated individual variables. It addresses the area of need, moving from cohort to patient, by translating disease patterns into individual treatment response. Importantly, we provide detailed information about the accuracy and robustness of the predictions, which is specific to each patient's individual scenario and treatment choice. The models will be made available to physicians in the form of a web-based tool and will be incorporated in the MSBase data entry software (where it will not request any additional data entry from the physicians in order to conduct a prediction) with the aim of providing supporting information to complement treatment decision process. Finally, the models provide a framework for implementation of novel molecular, genetic and radiological modifiers of treatment effect into a comprehensive predictive algorithm.

Acknowledgements

We wish to thank all patients and their carers who have participated in this study and who have contributed data to the MSBase cohort. The list of MSBase Study Group co-investigators and contributors is given in the online supplement.

Funding

This study was financially supported by National Health and Medical Research Council (practitioner fellowship 1080518, project grants 1129189, 1083539 and 1032484 and centre for research excellence 1001216) and University of Melbourne (Faculty of Medicine, Dentistry and Health Sciences research fellowship). The MSBase Foundation is a not-for-profit organization that receives support from Biogen, Novartis, Merck, Roche, Teva and Sanofi Genzyme. The study was conducted separately and apart from the guidance of the sponsors.

Conflict of interest

T.K. served on scientific advisory boards for Roche, Genzyme, Novartis, Merck and Biogen, has received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi, Genzyme, Teva, BioCSL and Merck and has received research support from Biogen. L.S. received research fellowship from Novartis and long term institutional support for research activities from the Faculty of Informatics and Statistics, University of Economics, Prague. T.S. received compensation for travel from Biogen. V.J. received conference travel support from Novartis and Merck Serono. D.H. received speaker honoraria and consulting fees from Biogen, Merck Serono, Teva and Novartis, as well as support for research activities from Biogen and research grants from Charles University in Prague (PRVOUK-P26/LF1/4 and Czech Ministry of Health (NT13237-4/2012). E.H. received speaker honoraria and consultant fees from Biogen, Merck Serono, Novartis, Genzyme and Teva, as well as support for research activities from Biogen, Merck Serono and research grants from Charles University in Prague (PRVOUK-P26/LF1/4 and Czech Ministry of Health (NT13237-4/2012). M.T. received speaker honoraria from Biogen-Idec, Bayer-Schering, Sanofi Aventis, Merck-Serono, Teva, Novartis and Almirall; has received research grants for her Institution from Biogen-Idec, Merck-Serono, and Novartis. G.I. received speaking honoraria from Biogen, Novartis, Sanofi, Merck Serono and Teva. A.L. is a Bayer, Biogen, Genzyme, Merck Advisory Board Member. She received travel grants and honoraria from Bayer, Biogen, Merck, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla (FISM). Her institution received research grants from Bayer, Biogen, Merck, Novartis,

Sanofi, Teva and Fondazione Italiana Sclerosi Multipla (FISM). M.G. received consulting fees from Teva Canada Innovation, Biogen, Novartis and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis and EMD Serono. He has also received a research grant from Canadian Institutes of Health Research. P.D. served on editorial boards and has been supported to attend meetings by EMDSerono, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme. P.G. is a Novartis, Teva-neuroscience, Biogen and Genzyme advisory board member, consultant for Merck Serono, received payments for lectures by Merck Serono, Teva-Neuroscience and Canadian Multiple sclerosis society, and received grants for travel from Teva-Neuroscience and Novartis. P.S. received travel grants and speaking honoraria from Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi/Genzyme and Teva. R.H. received honoraria as consultant on scientific advisory boards from Merck-Serono, Biogen, Genzyme-Sanofi and Teva, research funding from Merck-Serono and Biogen, and speaker honoraria from Sanofi-Genzyme and Novartis. F.G-M. received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi and ONO Pharmaceuticals. H.B. served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck Serono, Novartis and Biogen. E.P. served on scientific advisory boards for Merck Serono, Genzyme and Biogen; he has received honoraria and travel grants from Sanofi Aventis, UCB, Lundbeck, Novartis, Bayer Schering, Biogen, Merck Serono, Genzyme and Teva; he has received travel grants and equipment from 'Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche'. C.B. received conference travel support from Biogen, Novartis, Bayer-Schering, Merck-Serono and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis. R.A. received honororia from Biologix, Biogen, Bayer, Genpharm, Genzyme, Merck-Serono, GSK and Novartis, and served on advisory board for Biologix, Biogen, Bayer, Genpharm, Genzyme, Novartis, Genzyme, Merck-Serono and Novartis. V.V-P. served on advisory boards for Biogen, Novartis Pharma and Sanofi-Genzyme; has received travel grants and consultancy fees from Biogen, Bayer Schering, Sanofi Aventis, Merck Serono, Sanofi-Genzyme and Novartis Pharma; has received research grants from Bayer Schering. J.L-S. accepted travel compensation from Novartis, Biogen and Merck Serono. Her institution receives the honoraria for talks and advisory board commitment and also clinic support from Bayer Health Care, Biogen, CSL, Genzyme Sanofi, Merck Serono, Novartis and Teva. M.T. received travel grants from Merck Serono, Novartis, Bayer-Schering, Merck-Serono and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis. R.B. received speaker honoraria from Bayer Schering, Biogen, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Teva; research grants from Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi-Aventis, Teva; congress and travel/accommodation expense compensations by Almirall, Bayer Schering, Biogen, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Teva. G.I. had travel/accommodations/meeting expenses funded by Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi Aventis, and Teva. F.G. served on scientific advisory boards for Biogen Idec, Novartis and Sanofi Aventis and received funding for travel and speaker honoraria from Biogen Idec, Merck Serono, and Almirall. D.S. received honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva and Merck-Serono. C.O-G. received honoraria as consultant on scientific advisory boards from Biogen, Bayer-Schering, Merck-Serono, Teva and Novartis; has participated in clinical trials/other research projects by Biogen, GSK, Teva and Novartis. M.S. has participated in, but not received honoraria for, advisory board activity for Biogen, Merck Serono, Bayer Schering, Sanofi Aventis and Novartis. R.A. received conference travel support from Novartis, Teva, Biogen, Bayer and Merck Serono and has participated in clinical trials by Biogen, Novartis, Teva and Actelion. F.V. is an advisory board member for Teva Biogen Merck Serono and Novartis. P.M. did not declare any competing interests. J.O. serves on scientific advisory boards for Biogen, Genzyme and Novartis; has received speaker honoraria from Biogen, Bayer-Schering, Genzyme, Merck-Serono, Novartis and Teva and research grants from Biogen, Merck Serono, Novartis and Teva. M.P.A. received honoraria as consultant on scientific advisory boards by Biogen, Bayer-Schering, Merck-Serono, Teva and Sanofi-Aventis; has received research grants by Biogen, Bayer-Schering, Merck-Serono, Teva and Novartis. S.H. received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering. C.R. received research funding, compensation for travel or speaker honoraria from Biogen, Novartis, Genzyme and Almirall. S.F. received research funding, speaker honoraria and compensation for travel from and served as a consultant on advisory board for Bayer-Schering, Teva, Biogen, Merck Serono, Genzyme and Novartis. E.C. received honoraria as consultant on scientific advisory boards by Biogen, Bayer-Schering, Merck-Serono, Genzyme and Novartis; has participated in clinical trials/other research projects by Merck-Serono, Roche and Novartis. C.R. received speaker honoraria from Bayer Schering, Novartis and Biogen, congress and travel expense compensations from Biogen, Teva, Merck Serono and Bayer Schering. F.M. participated in clinical trials sponsored by EMD Serono and Novartis. J.L.S-M. accepted travel compensation from Novartis and Biogen, speaking

honoraria from Biogen, Novartis, Sanofi, Merck Serono, Almirall, Bayer and Teva and has participated in a clinical trial by Biogen. M.B. served on scientific advisory boards for Biogen, Novartis and Genzyme and has received conference travel support from Biogen and Novartis. He serves on steering committees for trials conducted by Novartis. His institution has received research support from Biogen, Merck-Serono and Novartis. J.H. received honoraria for serving on advisory boards for Biogen, Genzyme and Novartis, and has received speaker's fees from Bayer, Biogen, Genzyme, Merck Serono, Novartis, and Teva Pharmaceuticals. He has served as principal investigator for projects sponsored by, or received unrestricted research support from Bayer, Biogen, Merck Serono, Novartis and Teva Pharmaceuticals. H.B. served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck Serono, Novartis and Biogen. A.M., A.P., V.S., S.V., and M.L.S did not declare any competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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