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Serum neurofilament light chain reflects inflammation-driven neurodegeneration and predicts delayed brain volume loss in early stage of multiple sclerosis

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Abstract

Background: Serum neurofilament light chain (sNfL) is a marker of neuroaxonal injury. There is a lack of studies investigating the dynamics of relationships between sNfL levels and radiological disease activity over long-term follow-up in multiple sclerosis (MS).

Objectives: To investigate the relationship among repeated measures of sNfL, lesion burden accumulation, brain volume loss and clinical measures.

Methods: We investigated 172 patients in the early stages of MS (McDonald 2017 criteria). Clinical exams were performed every 3 months and brain magnetic resonance imaging (MRI) scans were collected annually over 48 months. sNfL levels were measured in serum by Simoa assay at the time of treatment initiation and then annually over 36 months.

Results: In repeated-measures analysis, considering all time points, we found a strong relationship between percentage changes of sNfL and lesion burden accumulation assessed by T1 lesion volume ($p < 0.001$) and T2 lesion number ($p < 0.001$). There was no relationship between percentage changes of sNfL and brain volume loss over 36 months ($p > 0.1$). Early sNfL levels were associated with delayed brain volume loss after 48 months ($p < 0.001$). Patients with No Evidence of Disease Activity (NEDA-3) status showed lower sNfL levels compared with active MS patients.

Conclusions: sNfL is associated with ongoing neuroinflammation and predictive of future neurodegeneration in early MS.

Keywords: Neurofilament light chain, neurodegeneration, inflammation, atrophy, lesion, multiple sclerosis

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Introduction

Inflammatory demyelination is thought to be a key pathological process in multiple sclerosis (MS), leading to axonal transection, neuronal loss and disability progression.[1] However, questions still exist about the origin and progression of neurodegenerative processes over the course of disease.[2–6] A number of recent studies suggest inflammation and neurodegeneration are simultaneous processes.[2,7,8] However, most studies emphasize neurodegeneration as a secondary phenomenon related to neuroinflammation.[1,9,10] Given that brain and spinal cord atrophy is strongly associated with disability progression, there is currently an urgent need for a simple, reliable biomarker of neurodegeneration in MS. Finding such a biomarker could play a key role in the prediction of disease course as well as in monitoring of treatment response.

Neurofilament light chain (NfL) levels have been suggested as a potential biomarker in MS.[11–15] Recent studies have shown a strong relationship between serum NfL (sNfL) levels and lesion burden as well as

future development of brain volume loss.[16–22] However, only a few studies have investigated the dynamics of relationship between sNfL levels and imaging measures over longer follow-up periods in multiple time points.[16,23] In this context, a detailed investigation of time-dependent relationship between sNfL levels and radiological disease activity has a potential to improve understanding of the aetiology and dynamics of sNfL increase in early MS patients. In order to implement sNfL in clinical practice, it must first be elucidated whether sNfL is a marker predominantly associated with ongoing inflammation (i.e. acute inflammation-driven neurodegeneration), or whether it is a marker preceding neurodegeneration in MS.

The aim of our study was to investigate the longitudinal relationship between sNfL levels and brain imaging markers including lesion burden and brain atrophy, as well as clinical measures, over long-term follow-up in a group of early MS patients.

Methods

Patients

From the original SET cohort (Study of Early Interferon beta-1a Treatment), 172 MS patients after first demyelinating event (according to McDonald criteria 2017) were included.[24,25]

The SET study was an investigator-initiated, observational, prospective multicenter clinical study in the Czech Republic. Patients were enrolled between October 2005 and July 2009. Inclusion criteria included age between 18 and 55 years, enrolment within 4 months from the first demyelinating event, Expanded Disability Status Scale (EDSS) score at baseline ⩽3.5, ⩾2 T2-hyperintense lesions on diagnostic magnetic resonance (MR) images (before corticosteroid treatment) and ⩾2 cerebrospinal fluid (CSF)-restricted oligoclonal bands (OCB) obtained at the screening prior to corticosteroid treatment (all patients were treated with 3–5 g methylprednisolone). Baseline brain MRI was acquired ⩾30 days after steroids and prior disease-modifying therapy (DMT) initiation. All patients started intramuscular interferon beta (IFNb)-1a once a week (30 mg; Biogen-Idec, Cambridge, MA, USA).[24,25] Patients were followed up for 48 months with evaluation of EDSS at baseline (DMT initiation) and then at every 3 months.[19]

The study protocol was approved by the Medical Ethics Committees of the General University Hospital in Prague and ethics committees in the participating centres. All patients provided written informed consent.

Blood sampling and sNfL measurement

Serum samples were collected on the same day as the clinical visits and stored at −80°C. Sampling procedures were performed according to the standard protocol.[26] Serum samples were assembled from screening (i.e. before corticosteroid treatment), at baseline (i.e. on a day of initiation of IFNb-1a), at month 1 and then annually over the next 36 months (i.e. at 12, 24 and 36 months).

sNfL concentration was measured using a sensitive immunoassay on the Simoa platform at the University Hospital Basel as described previously.[16,17,27,28] Inter-assay coefficients of variation (CVs) for three native serum samples were below 10% (i.e. 7.8%, 8.8% and 5.5% for 7.0, 18.8 and 81.3 pg/mL, respectively). The mean intra-assay CV of duplicate determinations for concentration was 6.4%. One patient's samples showed an sNfL value below 1.3 pg/mL (i.e. the lower limit of quantification). This patient was excluded from the analysis. Measurements were performed on coded samples. All laboratory personnel had no access to clinical data and remained blinded to treatment allocation and diagnosis.

Imaging

This study used brain MRI scans performed at baseline and at 12, 24, 36 and 48 months of follow-up. A standardized protocol was performed on a 1.5-T MRI scanner (Gyroscan; Philips Medical Systems, Best, The Netherlands) and consisted of two sequences: fluid-attenuated inversion recovery (FLAIR) and T1-weighted three-dimensional turbo field echo (T1-WI/TFE 3D). In addition, patients underwent post-contrast T1 spin echo (SE) 3-mm slice thickness scans 5 minutes after contrast injection of a single dose of 0.1 mmol/kg of Gd-DTPA with TE/TR (echo time/repetition time) = 12/450 ms. Acquisition parameters for the sequences were as follows for FLAIR: TE = 140 ms, TR = 11,000 ms, inversion time (TI) = 2600 ms, flip angle (FA) = 90°, field of view (FOV) = 256 mm and 3D-T1: TE = 5 ms, TR = 25 ms, FA = 30°, FOV = 256 mm. All MRI scans were performed on a single MRI scanner in the General University Hospital in Prague. MRI scans were performed ⩾30 days after corticosteroid treatment. Semi-automated image analysis of the whole brain (WB), brain parenchymal fraction (BPF), corpus callosum (CC) volume loss, T2 lesion volume (T2LV) and number, and T1 lesion volume (T1LV) was performed with the ScanView software.[29] The presence and number of gadolinium-enhancing lesions (GAD lesions) was established on post-contrast images by visual inspection of experienced neuroradiologist.

Enhancing lesions were confirmed by the simultaneous presence of hyperintense lesions on FLAIR images. Grey matter volume (GMV) and white matter volume (WMV) were analysed using SIENAX (http://www.fmrib.ox.ac.uk/analysis/research/siena/). Regional brain volumes were normalized with respect to the total intracranial brain volume (ICV) (calculated as the sum of the total brain volume and the total intra-ventricular CSF volume). Normalized compartment volumes were calculated, as follows: BPF = WMV + GMV/ICV; GM fraction = GMV/ICV and CC fraction = CC/ICV.

In the validation analysis of the ScanView with commonly used volumetric techniques, we obtained following intraclass correlation coefficients: 0.87 for T2LV (Jim), 0.82 for T2LV absolute change (Jim), 0.95 for WB volume (SIENAX) and 0.75 for WB percentage volume change (SIENA).[29] Scan-rescan error of ScanView was 0.3% for WB volume loss, 0.25% for BPF, 0.7% for CC and 0.25 mL for lesion volume.

Statistical methods

All analyses were performed using the R statistical system (http://www.R-project.org).

Relationships between sNfL levels at different time points as well between sNfL and baseline parameters (MRI and clinical) were evaluated using Spearman correlation test. The longitudinal relationship between percentage changes of sNfL levels (change between months 1 and 12, months 1 and 24, months 1 and 36) and changes of MRI and clinical parameters (change between months 0 and 12, months 0 and 24, months 0 and 36) were explored. sNfL levels at month 1 were used as a baseline instead of sNfL levels at month 0 due to a high proportion of missing sNfL data at baseline and strong linear relationship between sNfL levels at months 0 and 1 (Supplementary Figure 1). Moreover, we observed highly variable sNfL levels at screening measured at the time or shortly after the first clinical event. This together with a longer time from baseline and weaker correlation with baseline sNfL levels argued against their use instead of the baseline levels. In validation analysis, sNfL level at screening was used as a baseline measure.

We applied adjusted log-linear mixed effect models with random intercept per patient fitted by maximum likelihood method (Supplementary Table 1). First, univariate models were conducted using logarithmically transformed relative change of sNfL from month 1 as the dependent variable and time from baseline, change of EDSS from baseline, cumulative number of relapses from baseline, absolute change of T1LV and T2LV from baseline, cumulative number of T2 lesions from baseline, number of GAD lesions at particular time points and percentage changes of WB, GM and CC volumes from baseline as explaining variables (one by one). Absolute changes of lesion volumes over time were used to prevent overestimation of relative increase in patients with low lesion load and marginal lesion volume accumulation. Akaike information criterion (AIC) was calculated for each univariate model.

Based on the results from the univariate models, taking into account the clinical importance and degree of collinearity between the above-mentioned explanatory variables, we defined a final multivariate log-linear mixed-effects model with random intercept per patient. In the final model, time from baseline, change of EDSS from baseline, cumulative number of relapses from baseline, cumulative number of T2 lesions from baseline, absolute change in T1LV and percentage change in WB volume from baseline were used as independent variables. The model fit was assessed via AIC and significance of each variable was computed using t-statistic.

To investigate a predictive role of sNfL levels in comparison with lesional pathology (number and volume), we also analysed the relationship between sNfL levels at month 1 and the evolution of MRI volumetric parameters over 48 months using multivariate linear regression adjusted for age and sex. We also analysed predictive role of sNfL levels from various time points.

Finally, we investigated the evolution of sNfL levels in patients with and without No Evidence of Disease Activity (NEDA-3) status over the follow-up.[30]

Results

Baseline characteristics

Table 1 provides basic demographic, clinical and MRI characteristics at baseline. Mean age of patients was 29 years (median 28 years) with the female/male ratio being 2:1. The mean time between disease onset and treatment initiation was 82 days (median 79 days).

All investigated cross-sectional atrophy MRI parameters, including BPF (rho = 0.08, $p = 0.338$), GM fraction (rho = 0.02, $p = 0.793$) and CC fraction (rho = –0.14, $p = 0.083$), were not associated with sNfL levels at month 1. The strongest relationship was found between

Table 1. Demographic, clinical and MRI characteristics at baseline.

Variable	Median (IQR)
Age at onset	28.00 (23.50–33.50)
Gender (female/male)	115/57
Time between onset and baseline (days)	79.50 (64.00–99.75)
EDSS	1.50 (1.5–2.0)
Whole brain volume (cm^3)	1184.00 (1117.40–1249.30)
Brain parenchymal fraction (%)	87.09 (85.83 –88.10)
Corpus callosum fraction (%)	0.32 (0.29–0.35)
Grey matter fraction (%)	44.60 (43.38–46.27)
T2 lesion volume (cm^3)	0.63 (0.21–2.01)
T1 lesion volume (cm^3)	0.48 (0.28–0.92)
T2 lesion number	6.00 (3.00–15.00)
Presence of GAD lesion at baseline	45 (27%)

IQR: interquartile range; EDSS: Expanded Disability Status Scale; GAD lesion number: number of gadolinium-enhancing lesions; MRI: magnetic resonance imaging.

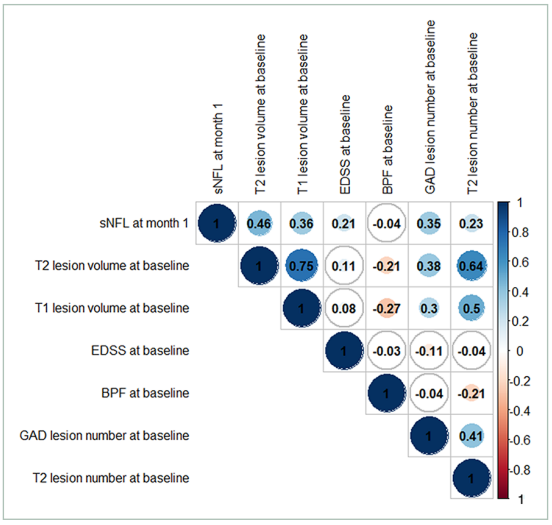

Figure 1. Correlogram of the relationships among serum neurofilament light chain levels at 1 month, clinical and MRI parameters at baseline.

sNfL levels and T2LV (rho = 0.46, $p < 0.001$). There was a weak association between sNfL and baseline EDSS (rho = 0.21, $p = 0.01$) (Figure 1 and Supplementary Table 2).

sNfL levels over follow-up

The highest sNfL levels were found at baseline (median: 22.68 pg/mL, interquartile range (IQR): 12.62–39.89 pg/mL) and the lowest sNfL levels at 36 months (median: 12.24 pg/mL, IQR: 8.96–16.49 pg/mL) (Supplementary Table 3). We found strong relationships among sNfL levels at different early time points, especially between baseline and the first month of the study (rho = 0.93, $p < 0.001$) (Supplementary Figure 1). However, early sNfL levels were only weakly associated with sNfL levels at later time points (Supplementary Table 4). At the group level, we observed a linear decrease in sNfL levels over time (Supplementary Figure 2).

Longitudinal relationship between sNfL levels and MRI and clinical parameters

The percentage changes of sNfL level over time (change between months 1 and 12, months 1 and 24, months 1 and 36) were most closely associated with T2LV absolute change ($p < 0.001$), T1LV absolute change ($p < 0.001$), increase in T2 lesion number ($p < 0.001$) (change between months 0 and 12, months 0 and 24, months 0 and 36) and number of GAD lesions at different time points (Table 2). A weak association was found between sNfL change and cumulative number of relapses ($p = 0.036$). In the multivariate model taking into the account all selected variables based on the results of univariate model, T1LV absolute change, T2 lesion number change and time from baseline were the best independent correlates of sNfL percentage change over follow-up (Table 3). In repeated-measures analysis, EDSS and percentage global and regional brain volume changes (between months 0 and 12, months 0 and 24, months 0 and 36) were not associated with percentage changes of sNfL (between months 1 and 12, months 1 and 24, months 1 and 36). Very similar results were observed, when sNfL levels were re-baselined at screening (Supplementary Table 5).

Table 2. The longitudinal relationships between percentage change of serum neurofilaments light chain (sNfL) levels (change between months 1 and 12, months 1 and 24, month 1 and 36) and change of clinical and imaging explanatory variables (change between months 0 and 12, months 0 and 24, months 0 and 36) analysed by univariate mixed-effects models.

Independent variable	Regression coefficient (unstandardized)	AIC	*p* value
Time from baseline	−0.044	612	0.094
EDSS absolute change	−0.03	609	0.454
Cumulative relapse number	0.058	606	0.036
T2 lesion volume absolute change	0.104	549	<0.001
T1 lesion volume absolute change	0.256	557	<0.001
Cumulative number of T2 lesions	0.062	548	<0.001
Number of GAD lesions	0.07	578	<0.001
Whole brain volume percentage change	4.273	603	0.148
Grey matter volume percentage change	1.314	603	0.183
Corpus callosum volume percentage change	0.654	605	0.557

AIC: Akaike information criterion; EDSS: Expanded Disability Status Scale; GAD lesions: gadolinium-enhancing lesions at particular time point.

Table 3. The longitudinal relationships between percentage changes of sNfL levels (change between months 1 and 12, months 1 and 24, months 1 and 36) and change of clinical and imaging explanatory variables (change between months 0 and 12, months 0 and 24, months 0 and 36) analysed by multivariate mixed-effects models.

Variable	Regression coefficient (unstandardized)	*p* value
Intercept	1.701	<0.001
Time from baseline	−0.083	0.003
EDSS absolute change	−0. 046	0.290
Cumulative relapse number	0.046	0.179
T1 lesion volume absolute change	0.241	<0.001
Cumulative number or T2 lesions	0.051	<0.001
Whole brain volume percentage change	5.231	0.094

EDSS: Expanded Disability Status Scale; sNfL: serum neurofilament light chain.
Akaike information criterion = 504.5.

Prediction of brain volume loss over follow-up by early neurofilament levels

We found a strong relationship between cross-sectional log-transformed sNfL levels at month 1 and percentage change of WB ($p < 0.001$), CC ($p < 0.001$) and GMV loss ($p = 0.001$) over 48 months. Percentage or absolute change of sNfL between screening and month 1 was not associated with imaging measures at 48 months. We did find a trend for stronger association between early sNfL levels (at screening, month 1 or 12) and WB volume loss but not BPF or T2LV at 48 months compared with later sNfL levels (month at 24 or 36) and MRI measures (Supplementary Table 6). In the multivariate models, sNfL was a stronger and independent predictor of brain volume loss than T1LV, T2LV, T2 lesion number or GAD lesion number. Results from the predictive models are summarized in Supplementary Table 7.

Low sNfL levels in patients with NEDA-3 over 48 months of follow-up

Patients who lost NEDA-3 status within 36 months showed higher sNfL levels over follow-up than patients with sustained NEDA-3 status. All five patients with sNfL levels >25 pg/mL at screening (or at baseline due to missing screening data), but NEDA-3 status after 36 months, lost their NEDA-3 status between 36 and 48 months (Figure 2). No patient with NEDA-3 status over 48 months had sNfL levels at screening over 25 pg/mL. Results remained identical whether or not GAD lesions were consider in NEDA status definition.

Discussion

sNfL is a promising biochemical biomarker of disease activity in MS. Although previous studies have

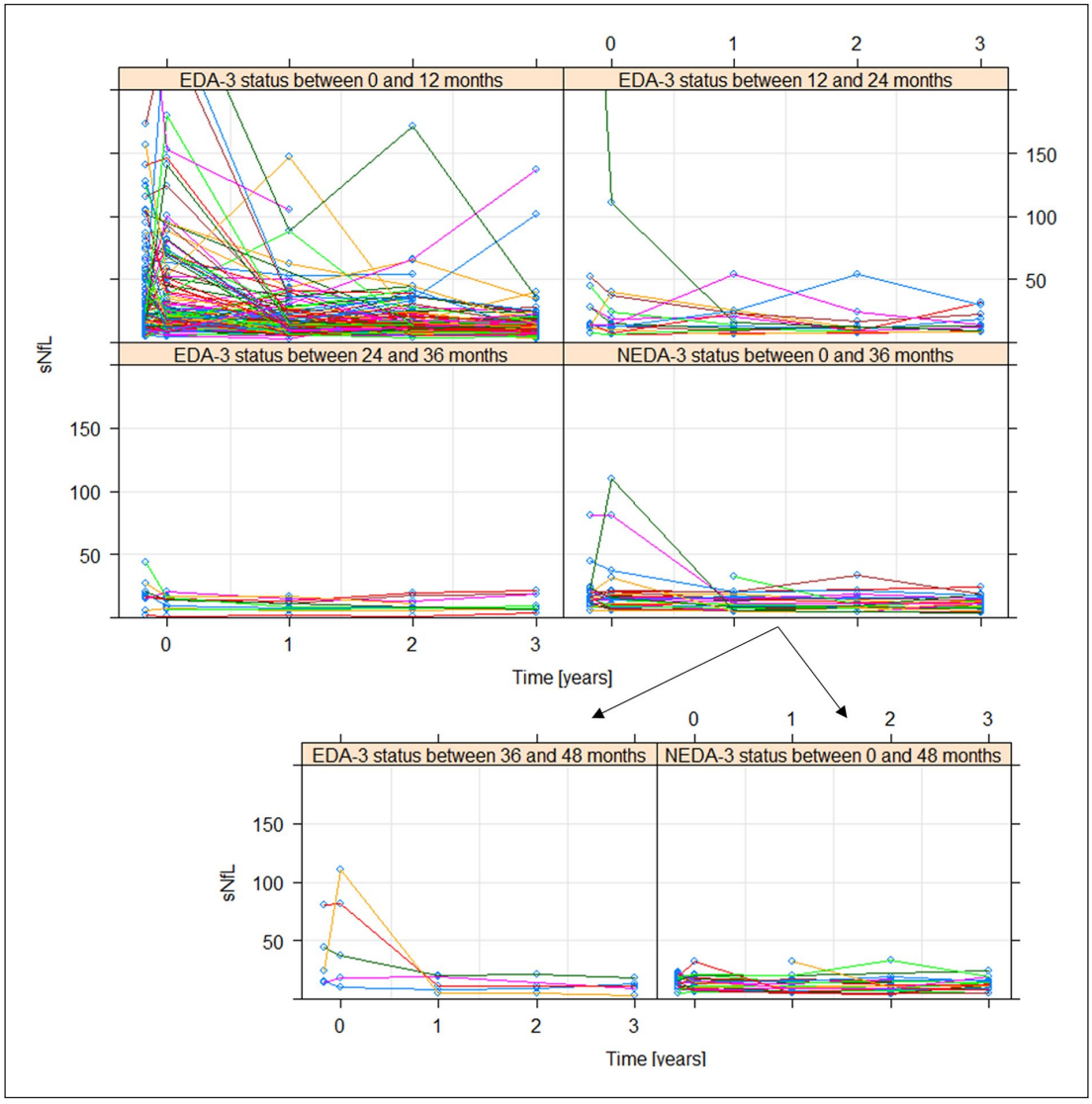

Figure 2. Serum neurofilament light chain levels in patients with evidence of disease activity-3 (EDA-3) and with no evidence of disease activity-3 (NEDA-3) status over follow up.

demonstrated strong relationships between sNfL levels and lesion burden and brain and spinal cord atrophy, there is limited information about time-dependent interactions among sNfL levels, lesion burden accumulation and brain atrophy over longer follow-up.[16,23]

From a clinical point of view, it is important to clarify whether an increase in sNfL levels in the early stages of MS is associated with neuropathological processes driven mainly by ongoing neuroinflammation, or whether it is rather a marker of preceding neurodegenerative processes.

In this study, we found a strong longitudinal relationship between change of sNfL levels and accumulation of T1LV and T2LV and T2 lesion number over time. A number of studies showed an association between sNfL and imaging measures, but only very few included multiple biochemical and imaging measures over a longer follow-up period.[16,23] In our study, we had available four concurrent sNfL and MRI measures over 36 months allowing us a more detailed investigation of the dynamics of relationships between sNfL and disease activity. Although it is considered that neurodegeneration is mainly inflammatory-driven in early MS,[8,31] to the best of our knowledge, this has not been shown explicitly in the context of sNfL yet.

We also found cross-sectional association between sNfL levels and lesion burden, which is in line with results of previous research.[16–19,22,32] sNfL levels were also reflective of future neurodegenerative processes

associated with delayed but not immediate brain volume loss, suggesting critical impact of early axonal damage on long-term neurodegenerative processes, as shown in previous research.[16,18,20,22] On the other hand, early relative or absolute sNfL change (between screening and month 1) was not associated with imaging outcomes. Surprisingly, there was no relationship between sNfL levels and previous or ongoing global and regional brain volume loss. In this respect, we suggest that sNfL levels in early disease stages reflect neuropathological processes driven mainly by ongoing neuroinflammatory activity. This is in an agreement with neuropathological studies showing very close association between inflammation and neurodegeneration in MS patients.[8] Hence, we hypothesize that the findings from our study provide indirect evidence that sNfL in early disease stages of MS is to the greater extent a marker of inflammation-driven than non-inflammatory-driven neurodegeneration. At a group level, we observed a decrease in sNfL levels over time, which is in agreement with recent studies and can be explained by treatment effects, and possibly regression to the mean.[17,21,28,32,33] Finally, we also showed lower sNfL levels in patients with NEDA-3 status over follow-up compared with active MS patients, which is in the line with recent results.[20]

Taken together, considering clinical relevance of early sNfL levels for future clinical and radiological disease activity, sNfL may in future qualify as a biomarker of disease activity and endpoint for clinical trials.[33]

A limitation of the present study was the sample composition consisted of early stage MS patients treated mostly with interferons, which limits generalizability of our results to the whole MS population. Therefore, further research investigating MS cohorts on different treatments and with various disease phenotypes is warranted. In addition, future studies on patients in progressive phases of disease are needed to confirm an anticipated and more important role of non-inflammatory-driven neurodegeneration in the later disease stages.

Due to a lack of sNfL data at baseline, we re-baselined our sNfL levels data to the first month of the study, showing strong correlation (rho = 0.93) with the baseline sNfL levels. In other words, for statistical purposes, sNfL levels at month 1 were considered as baseline sNfL levels. Considering a decrease in sNfL levels following treatment initiation, slightly lower levels of sNfL after 1 month of treatment were expected. Given that we analysed percentage changes of sNfL, lower absolute sNfL levels at re-baselined month 1 should not play an important role in our longitudinal analysis.

Importantly, it is well known that sNfL levels reflect only recent or ongoing neuropathology and are not sensitive to the neuroaxonal injury occurring before more than 6–9 months.[14,21,34] In addition, fluctuation of sNfL levels over time due to dynamic disease activity may occur.[16,23] In this respect, a more frequent sNfL sampling would have the potential to increase a strength of association between sNfL levels and measures of ongoing neuroinflammation and also provide more relevant information for clinical practice.

Finally, given that MRI measures assessed in the study provide only indirect evidence to distinguish between inflammatory and non-inflammatory processes, confirmation of our results warrants further investigation.

Strengths of the present study were the large sample size, relatively long follow-up duration and the clinical homogeneity of the cohort. All patients were newly diagnosed with MS after first demyelination event, had ⩾2 OCB in the CSF, ⩾2 T2-hyperintense lesions on diagnostic brain MRI and initiated the same DMT. Importantly, the observation that increased levels of sNfL are associated especially with ongoing neuroinflammation rather than recent accelerated brain volume loss could not be proven using only two longitudinal time points as available in previous studies.

Conclusion

Increased levels of sNfL in early MS stages reflects neuropathological processes driven mainly by ongoing neuroinflammation as indirectly assessed by the accumulation of lesion burden. In addition, sNfL levels have a stronger association with future development of brain atrophy than with actual or previous brain volume loss.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: B.S. received compensation for travelling and conference fees from Novartis, Sanofi Genzyme, Biogen Idec and Roche as well as support for research activities from Biogen Idec. C.B. received conference travel grant from Teva and Novartis. Z.M, T.H., L.N. and J.K. report no disclosures. T.U. received financial support for conference travel and honoraria from Biogen Idec, Novartis, Genzyme, Roche and Merck Serono as well as support for research activities from Biogen Idec and Sanofi. M.V. received compensation for travel, speaker

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Supplemental Material

Supplemental material for this article is available online.

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Clinical trial

Initiation of first disease-modifying treatment for multiple sclerosis patients in the Czech republic from 2013 to 2016: Data from the national registry ReMuS

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ABSTRACT

Background: : Proper management of multiple sclerosis (MS) requires feedback from clinical practice via registries.
Objective: : To introduce the Czech national multiple sclerosis registry, ReMuS, and explore the availability and use of disease-modifying drugs (DMD).
Methods: : The analysis focused on patients who started their first DMD, either with first-line or second-line medication and was based on reimbursement criteria set by Czech regulators. Baseline information was used to predict relapses after DMD initiation and to compare patients that started DMD in different years.
Results: : A total of 3,328 patients started DMD treatment for MS between 2013 and 2016; 3,203 on first-line and 125 on second-line medication. The proportion of patients starting on second-line drugs increased from 1.8% in 2013 to 4.7% in 2016. The occurrence of a relapse within one year of DMD initiation was significantly related to (1) the Expanded Disability Status Scale (EDSS) score immediately prior to starting DMD and (2) the number of previous relapses. Both parameters were significantly lower in patients starting in later years of the explored interval.
Conclusion: : Data from the ReMuS registry highlights improvements made in the management of MS in the Czech Republic. However, a relatively low percentage of patients started treatment using second-line drugs, in contrast to trends in other countries.

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1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) that primarily affects younger individuals. While the course of the disease varies greatly, ranging from mild to severe, data from natural history studies clearly show pronounced neurological deterioration, within 10–20 years, in the majority of untreated patients.

Disease management has significantly changed during the last 20 years. Currently, more than 10 different disease-modifying drugs (DMD) with different efficacy and safety profiles are available (Giovannoni, 2018). However, an individually tailored approach, i.e., choosing the right drug for the right patient, remains complicated, since reliable prognostic and monitoring tools are lacking. Moreover, clinical decision-making relies mostly on data from randomized control trials (RCT), where patients are often treated under different conditions than those found in clinical practice (Sormani and Bruzzi, 2015).

To fill this gap, efforts have been made to collect data from real-world settings, i.e., from registries (Kalincik and Butzkueven, 2016; Trojano et al., 2017; Ziemssen et al., 2016) http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/10/WC500236644.pdf. Registry data can (1) help to better understand the behavior of a drug under real-world conditions, (2) provide long-term data, which are unavailable in RCTs, and (3) be used to compare different drugs combinations and sequencing therapy. Registry data can also assist regulators and state institutions responsible for treatment reimbursement since the cost-effectiveness of biological treatment remains an important issue. Furthermore, many countries, including many in Europe, still do not reimburse all MS drugs or they restrict the order in which drugs can be administered thus causing delays in initiating effective treatment (Berger et al., 2018; Kobelt et al., 2017). Paradoxically, this cost-saving technique may lead to higher treatment costs in the long run due to increased patient disability costs that are associated with delayed treatment.

The Czech Republic is a country with a population of about 10.6 million, of whom approximately 20,000 have been diagnosed with MS. Most of these patients (approx. 80–85%) are followed by one of 15 specialized MS centers across the country, a method that is consistent with current trends (Soelberg Sorensen et al., 2018). Access to biological treatment in the Czech Republic is defined by 2 conditions: 1) the rules under which the drug was registered in the European Union, and 2) the specific Czech reimbursement criteria, which are, in most cases, stricter than the registration criteria in the European Union. In light of new diagnostic criteria (Thompson et al., 2018), it is important to note that an examination of cerebrospinal fluid is a standard diagnostic procedure in the Czech Republic with oligoclonal band positivity being among the most important reimbursement criteria. In the Czech Republic, patients meeting the reimbursement criteria can be treated using first-line drugs (interferons, glatiramer acetate, and teriflunomide). These can be prescribed to newly diagnosed patients immediately after the first relapse. For prescription of second-line DMDs (dimethyl fumarate, fingolimod, natalizumab, and alemtuzumab) at least 2 moderate or severe relapses during the previous year are required. Based on this stratification, three distinct subgroups of patients emerge: (1) Patients who initiated first-line DMD immediately after the first relapse, (2) Patients who initiated first-line DMD after 2 or more relapses, and (3) Patients who initiated second-line DMD after at least 2 moderate or severe relapses during the previous year.

This paper has two main objectives: (1) to briefly introduce the Czech national MS registry, ReMuS, which has been collecting data from MS patients prospectively since 2013, and (2) to provide information about the availability and trends in biological treatment initiation in treatment naïve or newly diagnosed patients in the Czech Republic from 2013 to 2016.

Table 2
Development of the ReMuS registry.

Date of data export	Number of participating centers	Number of exported patients
30.06.2013	3	1501
31.12.2013	7	2920
30.06.2014	12	4715
31.12.2014	12	5796
30.06.2015	13	8310
31.12.2015	13	9406
30.06.2016	14	10,502
31.12.2016	15	11,498
30.06.2017	15	12,199
31.12.2017	15	13,003

2. Methods

2.1. The ReMuS registry

The Czech national registry of Multiple Sclerosis (ReMuS) was founded in 2013 and is operated by an independent organization, the Endowment Fund IMPULS, in collaboration with the Czech Neuroimmunological Society. The registry collects data on patients with MS from all 15 specialized MS centers in the Czech Republic. The main parameters collected and analyzed in the ReMuS registry are listed in Table 1. Data is collected using standardized software, iMed, and exported from each center every six months. In addition, data undergoes a multiple-level quality control process. Quality control reports are sent back to the MS centers to confirm suspicious, invalid, or missing information, which is subsequently corrected locally. The complete data set is then subjected to a thorough analysis, which is then summarized into semi-annual, descriptive reports giving an overview of the current situation. These reports are publicly available at www.multiplesclerosis.cz.

Until 2015, the registry's semi-annual reports focused only on data from patients treated using DMDs that could only be prescribed by the 15 specialized MS centers. Since 2015, the registry gathers and analyses data from all treated and untreated MS patients monitored by the MS centers. Through December 31, 2017, the registry collected data from 13,003 patients, which is more than an eightfold increase from the first data export in 2013 (see Table 2).

This project was approved by the designated ethics committees in all participating hospitals, and all patients signed an informed consent form.

2.2. Patient selection and data acquisition

This work describes patients who started their first DMD therapy

Table 1
The main parameters in the Czech national registry ReMuS.

Demographic parameters	Birth Date, Gender, Region of permanent residence, Date of death, Pregnancy
MS-related parameters	Date of MS onset, Expanded Disability Status Scale, including functional subsystems, Relapses including severity and form of treatment, Selected laboratory parameters
Treatment-related parameters	DMD/IVIG medication, Symptomatic treatment, Adverse events related to MS treatment
Socio-economic parameters	Individual healthcare insurance company, Employment status, Social benefits

MS: Multiple Sclerosis; DMD: Disease Modifying Drugs; IVIG: Intravenous Immunoglobulins;.

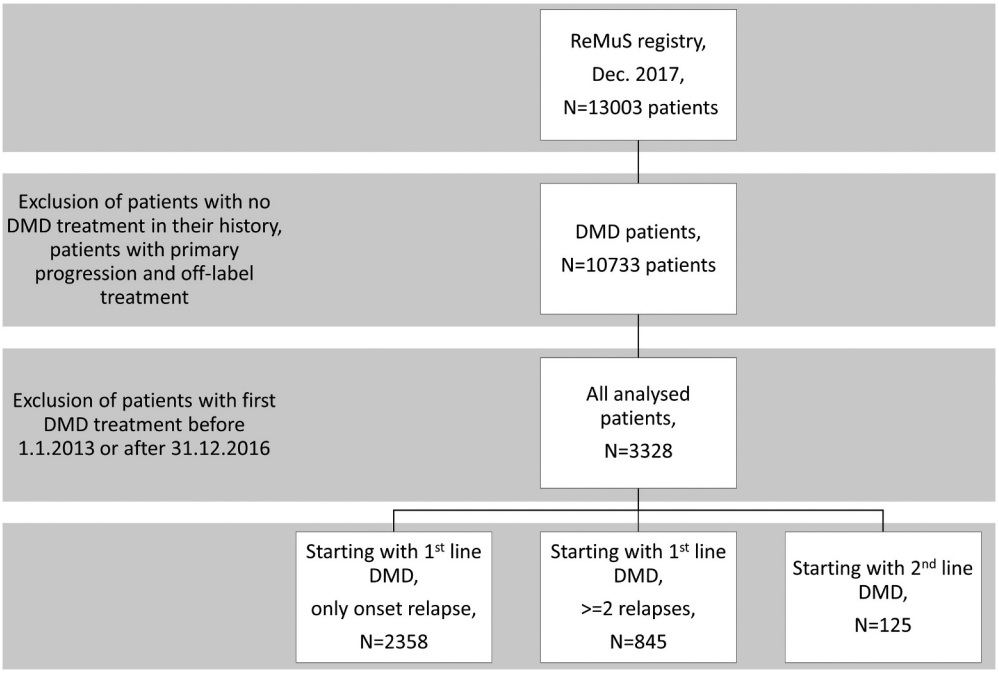

Fig. 1. Flowchart of patient disposition.

between 2013 and 2016. This period provided us with the highest quality data due to data having been (1) collected prospectively, (2) back-traced, and (3) repeatedly quality controlled since 2013. The seven monitored DMDs were interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab, and alemtuzumab. Therefore, only patients who initiated one of the above-mentioned DMD treatments between the years 2013 and 2016 were included in the analysis.

Stratification of patients was done using current Czech reimbursement criteria, which are set by the national regulator. Based on these criteria, we divided patients relative to their first DMD into 3 groups:

First-line DMD treatment (i.e., interferon beta, glatiramer acetate, and teriflunomide) was divided into 2 subgroups: (1) Patients that started after the first clinical relapse (First-line 1R) and (2) Patients with at least 2 relapses before initiating DMD treatment (First-line ≥2R). The third subgroup included patients who started DMD treatment using a second-line drug (i.e., dimethyl fumarate, fingolimod, alemtuzumab, and natalizumab); dimethyl fumarate is considered to be a second-line treatment in the Czech Republic.

Variables included in our analysis were: gender, date of birth, date of disease onset, date of death, lost to follow-up, DMD name, DMD start date, EDSS score at each visit, and date of each reported relapse.

2.3. Statistical analysis

Statistical analysis was conducted using R (version 3.4.0). The first step was to analyze basic demographic and clinical measures of the patients in the registry exported in December 2017. In addition, subgroups of patients who started their first DMD treatment between the years 2013 and 2016 were investigated. Descriptive statistics were computed as (1) percentages and numbers of events for binary and categorical variables, (2) mean and the sum of occurrences for count variables, and (3) mean and standard deviation (SD) for continuous variables. In cases where continuous variables had a highly skewed distribution, the median is also presented.

In step two, we examined the relationship between the percentage of patients with relapses within the first year after DMD treatment initiation and the remaining covariates. Dependency was modelled using multivariate logistic regression, with the relapse event as an outcome and the following as predictive variables: the age at the first recorded visit, time between disease onset and initiating DMD (i.e., groups < 3, 3–12, and > 12 months), sex, the average EDSS score value 1 year before initiating DMD, the number of previous relapses (i.e., binary, only at onset, or more), and the particular first DMD preparation (i.e. IFN, glatiramer acetate, and teriflunomide represented by 8 different brand names). The model fit was evaluated using the Hosmer and Lemeshow goodness of fit test. The importance of each covariate was examined using the likelihood ratio test and was interpreted in terms of the odds ratio (OR).

Based on a previous analysis, we explored differences in covariates affecting the relapse rate between patients starting treatment in specific years (e.g., 2013 vs. 2014). For each year, we described patients starting treatment and compared them with cohorts from other years. Descriptive statistics were constructed in the same manner as for the whole population. Moreover, tests comparing measures between years were performed. P-values were derived from an analysis of variance for continuous variables and the Chi-squared test for binary variables. Changes of patients' characteristics between years were confirmed using Kaplan-Meier curves for time to the first relapse after DMD initiation. Curves were compared using the log rank test.

Finally, the evolution of treatment strategies in the Czech Republic was described in proportion to each group (First-line 1R, First-line ≥ 2R, Second-line) for each year of the DMD initiation.

3. Results

3.1. Group-wise demographic characteristics

The total number of patients included in the registry as of the December 2017 export was 13,003 (Fig. 1). Of these patients, 10,733 were treated with DMDs, and 2270 were without DMD treatment. For the purpose of our detailed analysis between cohorts starting their first DMD between 2013 and 2016, we used data from 3328 patients. There are distinct differences between the 3 subgroups we analyzed. Table 3 presents an overview of baseline characteristics, together with a description of disease progression. Patients who initially started on second-line therapy tended to be younger, with a higher EDSS scores, and longer disease duration at the start of the DMD treatment. Due to

Table 3
Summary characteristics for different treatment strategies and the number of prior relapses for patients starting their first DMD between the years 2013 and 2016.

DMD type		First-line DMD		Second-line
		First-line 1R	First-line ≥2R	
N of patients		2358	845	125
Age at onset of MS [years]	Mean ± SD	33.39 ± 9.96	32.15 ± 9.66	29.03 ± 9.22
Gender	% males	30.3	26.3	37.6
EDSS score at first recorded visit	Mean ± SD	1.94 ± 0.93	2.21 ± 1.03	2.92 ± 1.43
	Median	2.0	2.0	2.5
EDSS score at start of first DMD	Mean ± SD	1.91 ± 0.93	2.43 ± 1.03	3.04 ± 1.47
	Median	2.0	2.5	2.75
Time from onset to start of DMD [years]	Mean ± SD	1.20 ± 3.19	5.61 ± 6.59	6.69 ± 6.76
	Median	0.36	2.96	3.77
N relapses before start of DMD (without post-onset relapses)	Mean ± SD	0 ± 0	2.10 ± 1.52	1.29 ± 1.65
Relapses 0–12 months after start of DMD	ARR	0.288	0.475	0.248
	Sum of relapses	665	397	31
	% of people with relapse[1]	21.1	34.9	18.4
	N of patients	486	291	23
Confirmed progression in EDSS score 0–12 months after start of DMD	% of patients[1]	5.6	6.9	5.0
	N of patients	112	51	6

DMD: Disease Modifying Drugs; R: relapse; MS: Multiple Sclerosis; SD: Standard Deviation; EDSS: Expanded Disability Status Scale; ARR: Annualized Relapse Rate;.
[1] out of the number of patients observed at least one year after DMD treatment initiation.

the low number of patients in the second-line therapy group ($N = 125$), no statistical comparison was possible. In this context, only first-line groups with complete follow-up data were used for further analysis.

3.2. Factors influencing the probability of continuing disease activity

The probability of having a new relapse one year after the start of a first-line DMD was significantly associated with the sex, age at first visit, the time between disease onset and DMD initiation, the EDSS score one year before starting DMD treatment, and the number of previous relapses (Table 4). Men were 23% less likely to have a relapse in the first year (OR = 0.77) than women. Similarly, with every one year older a patient was at the first recorded visit the chance of having a relapse, in the first year, was 3% lower (OR = 0.97); each EDSS point increased the chance of having a relapse during the first year by 39% (OR = 1.39), and patients without relapse activity after disease onset were 63% less likely to have a relapse during the first year of treatment than patients with multiple relapses (OR = 0.37). The Hosmer and Lemeshow test for model fit was non-significant ($p = 0.320$).

3.3. Evolution of early detection and early start of treatment in the Czech Republic

The number of patients starting their first DMD in each year did not differ in terms of demographic characteristics (i.e., the age at first visit and sex proportion remained the same, meaning that there was no change in the epidemiology characteristics of MS). However, there was a significant improvement in terms of early diagnoses and early treatment (i.e., EDSS scores when starting the first DMD and the number of previous relapses), as shown in Table 5. There were also differences in the time to first relapse after starting DMD between patients starting therapy in 2013 and 2016 (Fig. 2), with a trend toward lower risks of further relapses.

3.4. Temporal changes in treatment strategy in the Czech Republic

From 2013 and 2016, more than 800 patients per year initiated DMD treatment (Fig. 3); for this descriptive analysis, we used the whole cohort of 3328 patients with available baseline data. In 2013, only 15 patients (1.8% out of 819) initiated DMD treatment using second-line drugs, although this number increased to 39 patients (4.7% out of 824) in 2016.

4. Discussion

The Czech national registry, ReMuS, is a new registry that has been enrolling patients since 2013, reaching a level of 13,003 patients in the latest data export (December 2017). The quick growth in the number of patients included in the registry reflects the effective collaboration between the Endowment Fund IMPULS (the owner and operator of the registry) and the professional neurological community, the centralized nature of care of MS patients in the Czech Republic (the 15 MS centers monitor approximately 80% of all MS patients in the country), the presence of a solid infrastructure and tools for data collection, and a diligent system of data quality control. Currently, the registry covers more than 90% of all patients treated with DMDs (10,733), with the rest being non-DMD patients who represent a mix of mostly primary and secondary progressive MS patients and patients with mild forms of the disease. With 13,003 patients included out of an estimated 20,000 nationwide MS patients, the registry ReMuS provides an excellent overview of MS care and evolution of real-world clinical practice in the Czech Republic.

Table 4
The probability of having a new relapse one year after the start of first-line DMD, p-value indicates the significance of covariates in the final logistic regression model.

Covariate		Coefficient	OR	95% CI for OR	P-value
Gender	Men vs Women	−0.266	0.77	[0.62;0.94]	0.012
Age at first visit		−0.027	0.97	[0.96;0.98]	< 0.001
Years to DMD from onset [months]	3–12 vs <3	−0.214	0.81	[0.64;1.02]	< 0.001
	>12 vs <3	−0.774	0.46	[0.33;0.64]	
EDSS score 1 year before DMD		0.328	1.39	[1.25;1.54]	< 0.001
Relapses (R) prior DMD	1R vs >=2R	−0.986	0.37	[0.29;0.48]	< 0.001
Type of the first line DMD medication					0.479

DMD: Disease Modifying Drugs; EDSS: Expanded Disability Status Scale; CI: Confidential Interval; OR: Odds Ratio;.
[1] variable is not significant and contains too many levels to present results of estimates.

Table 5
Comparison of characteristics of first-line patients starting first DMD in each of the years 2013–2016, p-values evaluate the difference in covariates between different starting years. For this analysis, only first-line groups of patients with complete follow-up data were used.

Year first DMD started		2013	2014	2015	2016	P-value
N of patients		745	744	754	746	
Gender	% males	30.9	27.6	27.9	29.4	0.467
Age at first visit [years]	Mean ± SD	34.71 ± 9.86	35.08 ± 10.13	35.23 ± 10.11	35.14 ± 9.98	0.755
Time from onset to start of DMD [years]	Mean ± SD	2.41 ± 4.60	2.24 ± 4.80	2.39 ± 4.70	2.29 ± 4.94	0.889
	Median	0.50	0.42	0.47	0.44	
EDSS score 1 year before DMD	Mean ± SD	2.15 ± 1.02	2.08 ± 0.98	1.97 ± 0.95	1.97 ± 0.91	0.002
N of previous relapses (without onset relapse)	Mean ± SD	0.66 ± 1.33	0.58 ± 1.25	0.65 ± 1.29	0.48 ± 1.10	0.018

DMD: Disease Modifying Drugs; EDSS: Expanded Disability Status Scale;.

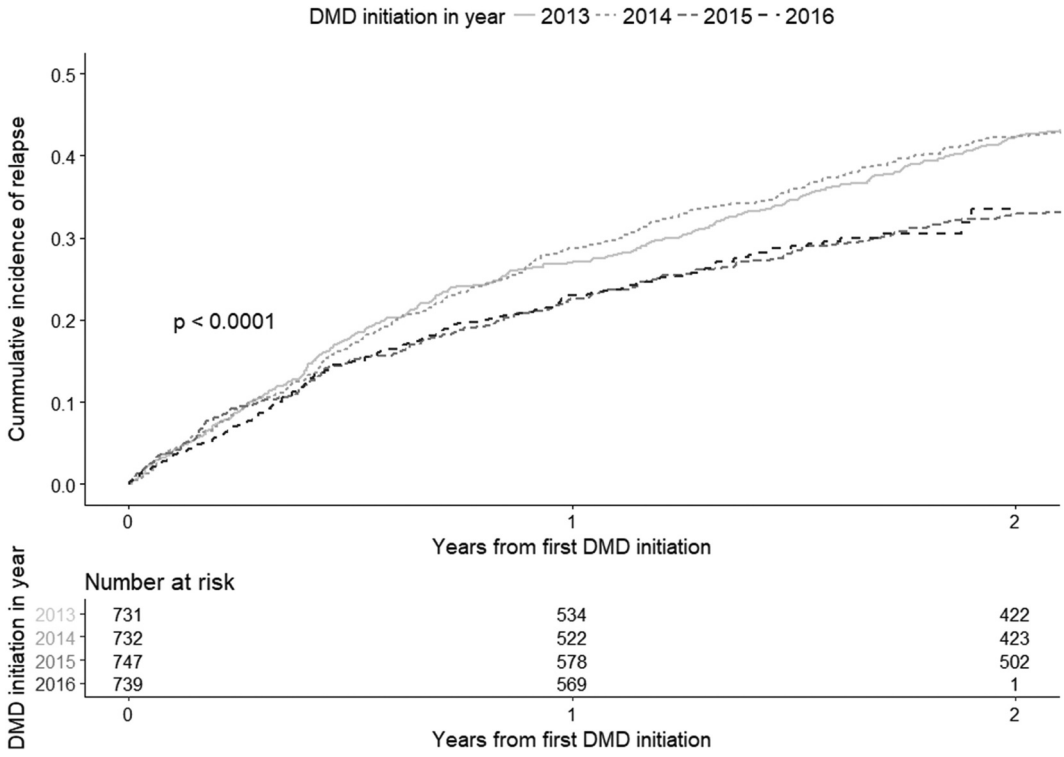

Fig. 2. Kaplan-Meier curves for time to first relapse after DMD initiation for cohorts of first-line patients starting in different years, p-value from log rank test is presented.

The current analysis aimed to describe DMD treatment initiation in the Czech Republic between 2013 and 2016. During these years, 3328 patients started their first DMD. This cohort represents a heterogeneous group of patients with the dominant subgroup consisting of 2358 patients who started their first DMD treatment immediately after their first relapse. These patients had a median disease duration of about 4 months.

The chance of having a relapse within one year after commencing treatment was significantly influenced by both the EDSS score 1 year before the start of DMD treatment and the number of relapses in the previous year, with both parameters increased the chance of relapse after starting treatment. This is in line with several other studies (Capra et al., 2017; Cerqueira et al., 2018; Chalmer et al., 2018) supporting the concept that early treatment initiation of patients with a lower disease burden may result in early disease stabilization. In contrast, the time between disease onset and treatment initiation was inversely associated with the risk of relapse, i.e., the shorter the time, the higher the risk of a future relapse. This may be explained by the heterogeneity of our sample, where patients with severe relapses and more aggressive disease tended to start DMD treatment earlier. The choice of first-line DMD treatment (i.e., IFN, GA and teriflunomide represented by 8 different commercial brands) did not have an effect on relapse activity, probably reflecting the comparative effectiveness of these drugs (Melendez-Torres et al., 2018).

A comparison of demographic and clinical parameters of subgroups of patients starting first-line DMDs in the years 2013–2016 showed a positive trend in the reduction of EDSS score and the number of relapses before the start of treatment. Even though the number of patients initiating treatment with a second-line DMD increased from 1.8% in 2013 to 4.7% in 2016, this increase was insignificant considering the large number of patients who had at least 2 relapses before DMD initiation. These patients could have benefited from a more aggressive DMD choice early in the disease course. Nonetheless, many received first-line treatment instead (26.7% in 2013 and 22.4% in 2016) (Kaunzner et al., 2016).

Our current analysis has several limitations. Since our stratification of patients depends on the number of relapses before starting DMD treatment, it may be affected by an incomplete record of relapses. A small number of patients initiating first-line treatment had only one recorded onset relapse, even though they may have experienced at least one unrecorded relapse. This becomes apparent when investigating patients with second line highly effective DMD therapy relative to the number of previously reported relapses. Twenty-six percent (26%) of these patients report only a single post-onset relapse, even though only

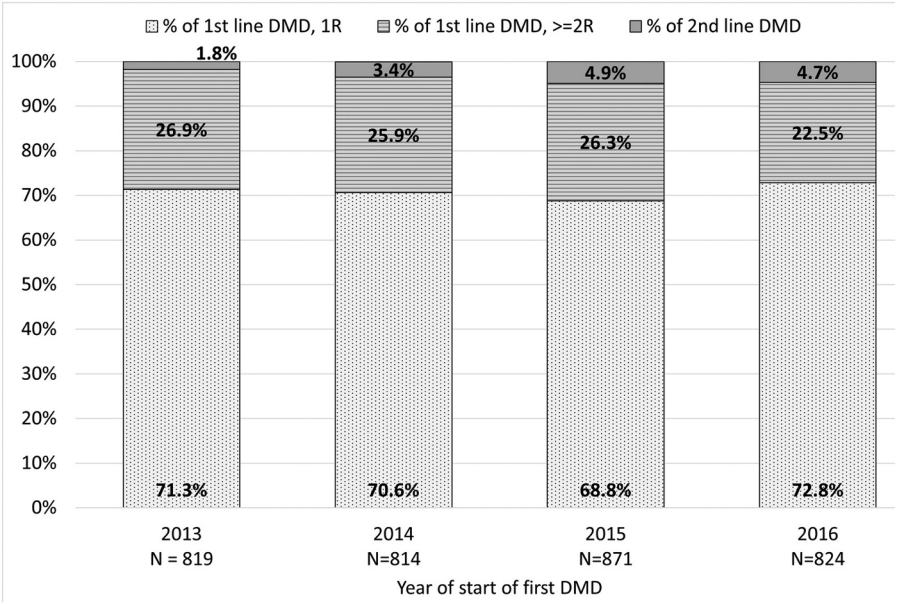

Fig. 3. Number of patients who started their first treatment in years 2013–2016 and their distribution in each year based on the type of first DMD and number of previous relapses (R), first-line DMDs include interferons, glatiramer acetate, and teriflunomide, second-line DMDs include dimethyl fumarate, fingolimod, natalizumab, and alemtuzumab.

patients with at least 2 relapses could, in theory, initiate with a second-line DMD treatment. Accordingly, this number could represent an estimate of the proportion of patients wrongly classified using the "single onset relapse" criterion.

Another potential limitation is that our statistical model, investigating the relationship between relapses one year after DMD initiation and the remaining covariates, might not include all possible confounders of these relationships. However, this weakness affects all exploratory analyses of registry data and cannot be avoided.

Finally, the observed trend of improvement of care in the Czech Republic could be based on a random peak in described characteristics. Only longer follow-ups can shed light on this.

5. Conclusion

We found, using data from the CZ national registry, ReMuS, a decrease in EDSS scores and the number of relapses prior to initial DMD treatment from 2013 to 2016 . This suggests that management of MS improved in the Czech Republic over the 2013–2016 period. This improvement could also be responsible for the decreased relapse-rate one year after DMD treatment initiation. Despite these positive trends, the rate of patients starting directly on second-line therapy is still low and does not correspond to the estimated number of patients with highly active MS, nor is it in line with treatment trends in countries with fewer economic restrictions.

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Declaration of Competing Interest

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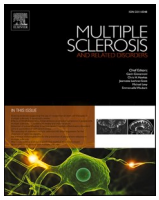

Does initial high efficacy therapy in multiple sclerosis surpass escalation treatment strategy? A comparison of patients with relapsing-remitting multiple sclerosis in the Czech and Swedish national multiple sclerosis registries

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ABSTRACT

Background: In relapsing-remitting multiple sclerosis (RRMS) the most common treatment strategy has been to start with low-moderate efficacy disease modifying therapy (LE-DMT) and to escalate to more efficacious treatments in cases of breakthrough disease activity. However, recent evidence suggests a better outcome in patients commencing with moderate-high efficacy DMT (HE-DMT) immediately after clinical onset.
Objective: The aim of this study is to compare disease activity and disability outcomes in patients treated with the two alternative strategies using the Swedish and Czech national multiple sclerosis registries, taking advantage of the fact that the relative frequency of each strategy differs markedly between these two countries.
Methods: Adult RRMS patients who initiated their first-ever DMT between 2013 and 2016 and were included in the Swedish MS register were compared with a similar cohort from the MS register of the Czech Republic using propensity score overlap weighting as a balancing method. The main outcomes of interest were time to confirmed disability worsening (CDW), time to achieve an expanded disability status scale (EDSS) value of 4,

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time to relapse, and time to confirmed disability improvement (CDI). To support the results, a sensitivity analysis focusing solely on patients from Sweden starting with HE-DMT and patients from the Czech Republic starting with LE-DMT was performed.

Results: In the Swedish cohort, 42% of patients received HE-DMT as initial therapy compared to 3.8% of patients in the Czech cohort. The time to CDW was not significantly different between the Swedish and Czech cohorts (p-value 0.2764), with hazard ratio (HR) of 0.89 and a 95% confidence interval (CI) of 0.77–1.03. Patients from the Swedish cohort exhibited better outcomes for all remaining variables. The risk of reaching EDSS 4 was reduced by 26% (HR 0.74, 95%CI 0.6–0.91, p-value 0.0327), the risk of relapse was reduced by 66% (HR 0.34, 95%CI 0.3–0.39, p-value <0.001), and the probability of CDI was three times higher (HR 3.04, 95%CI 2.37–3.9, p-value <0.001).

Conclusion: The analysis of the Czech and the Swedish RRMS cohorts confirmed a better prognosis for patients in Sweden, where a significant proportion of patients received HE-DMT as initial treatment.

1. Introduction

Multiple sclerosis (MS) is considered a lifelong incurable disease. However, over the last decades, the use of disease modifying therapies (DMTs) in relapsing-remitting MS (RRMS) has improved the clinical course. The therapeutic goal is to reduce disease activity and disability progression as much as possible. The main strategy has been to start treating patients with a low-moderate efficacy DMT (LE-DMT), and to escalate to a more efficacious DMT in patients presenting breakthrough in disease activity. However, early initiation of moderate-high efficacy DMTs (HE-DMTs) has been suggested as a better approach (Stankiewicz and Weiner, 2020). Several lines of evidence (Wiendl et al., 2021; Cree et al., 2022) support the use of this strategy to delay subsequent worsening of disability and transition to secondary progressive MS. It has also been suggested that early intervention with HE-DMTs may even improve neurological status and function in some patients.

To evaluate which strategy is more appropriate to achieve the best therapeutic results, multiple studies (Brown et al., 2019; Iaffaldano et al., 2021; He et al., 2020; Simonsen et al., 2021) based on real-world registry data have been conducted. Although the results have in general favored the early HE-DMT strategy, more studies are needed to confirm these conclusions, as differences in population characteristics and statistical methodology, as well as selection bias, may have impacted the outcome.

Recently, the Danish and Swedish registries conducted a comparison of their large cohorts of RRMS patients (Spelman et al., 2021). The MS patient populations of these two countries are very similar, which makes a comparison of treatment strategies plausible. In Sweden, the initial HE-DMT strategy is preferred by a significant part of physicians. In contrast, almost all patients in Denmark initiated treatment with LE-DMTs. This comparison showed better outcomes in patients with early initiation of HE-DMT.

To confirm the conclusions derived from the Denmark-Sweden comparison, we decided to compare the data from the Czech and Swedish MS registries. In the Czech Republic, the situation was similar to that of Denmark up to 2022, when the reimbursement criteria changed. The escalation strategy has been highly supported based on the reimbursement criteria, and therefore the vast majority of MS patients included in the Czech national registry received LE-DMTs as initial therapy. Furthermore, the threshold for treatment switch to a more efficacious DMTs is higher than in Sweden, as the criteria for escalation of DMT in the Czech Republic require at least one clinical relapse. In this study, we aimed to evaluate the same outcomes assessed in the Denmark-Sweden comparison, performing the comparison on similar cohorts of patients but with the added advantage of a longer follow-up period.

2. Methods

2.1. Data collection

The Swedish MS registry has been active since 2000, and has a coverage of more than 80% of the estimated MS population in the country (Hillert and Stawiarz, 2015). The Czech national MS registry (ReMuS) was established in 2013 and includes data from all of the 15 specialized MS centers in the Czech Republic (Horakova et al., 2019). Data collection was approved by the Swedish Ethical Review Authority and the designated ethics committees in all participating hospitals in the Czech Republic. All patients from the Czech registry signed an informed consent for data collection and evaluation. Consent in the Swedish MS registry is automatically provided by the first inclusion of a patient in the registry. This consent extends to any study that uses data sourced from the Swedish MS registry, and no additional procedures to obtain informed consent are required.

2.2. Inclusion criteria

Relapsing-remitting MS (RRMS) patients who initiated their first DMT between January 1st, 2013, and December 31st, 2016, were included in the analysis. The study focused on adults aged 18 to 55 years. Older patients were excluded to minimize the influence of comorbidities on outcomes. Patients with progressive MS at the time of the initiation of the first DMT were excluded.

2.3. Definitions and outcomes

The initiation of the first DMT was considered the study baseline. All expanded disability status scale (Kurtzke, 1983) (EDSS) measurements recorded within 90 days from relapse were excluded from the analysis of EDSS outcomes.

The primary endpoint was time to confirmed clinical disability worsening (CDW), defined as an increase from baseline EDSS by 1 point (or by 1.5 points when baseline EDSS was 0, and by 0.5 when baseline EDSS was 5.5 or above). CDW should have been confirmed by two consecutive visits, with a minimum interval of at least six months (Kalincik et al., 2015).

Secondary endpoints included annualized relapse rate (ARR), time to first relapse, time to EDSS 4 (evaluated only for patients with baseline EDSS below that value) and time to treatment switch (to any other DMT with a different mechanism of action). The reasons for the treatment change were unified between the registries and described. As a secondary endpoint, confirmed clinical disability improvement (CDI) was also analyzed for patients with baseline EDSS values of 2 or above. CDI was defined as an improvement from baseline EDSS by at least 1 point, or at least 0.5 point when the baseline EDSS value was 6 or above. This improvement should have been sustained for at least two consecutive visits, separated by at least six months.

The DMTs were grouped as low-moderate efficacy (dimethyl fumarate, glatiramer acetate, interferon beta-1a, interferon beta-1b, pegylated interferon beta-1a, teriflunomide) and moderate-high efficacy (alemtuzumab, fingolimod, natalizumab, ocrelizumab, ponesimod, rituximab).

2.4. Statistical analysis

All continuous baseline characteristics were described as mean plus standard deviation (SD), using the *t*-test for comparison between registries and absolute standardized differences (SDif). The discrete variables were quantified by counts and percentages and compared using the Chi-square test without continuity correction. EDSS values were described also as median plus interquartile range (IQR).

At first, we balanced the Swedish and the Czech patients in terms of the most important baseline characteristics using propensity score overlap weighting (Mlcoch et al., 2019). The weighting was used over a propensity score matching to include all patients from both registries, but to assure balance in the most important factors. Using matching instead of weighting, only subgroups of patients would be analyzed. The propensity score overlap weighting assures the mean values of characteristics selected for the model are equal between the two groups. The propensity score model consisted of age, gender, duration of the disease, baseline EDSS and ARR 12 months before the study baseline.

Only patients with calculated weights (all available characteristics for the models) were included in the analysis and thus described in the paper.

Initially, we focused on the comparison of entire cohorts, to make our results comparable with those reported in previous studies. However, since not all the patients included in the Swedish registry received HE-DMT as initial therapy, we performed an additional comparison between patients from the Swedish registry that received HE-DMT as initial therapy versus patients from the Czech registry that received LE-DMT as initial therapy. Therefore, two independent propensity score models were fitted. In the first case, weights for all Czech vs. Swedish patient comparisons were calculated, whereas in the second case weights for the Swedish patients that received HE-DMT and the Czech patients that received LE-DMTs were estimated.

Time-to-event outcomes were analyzed using a weighted Cox proportional hazards model, resulting in a hazard ratio (HR) estimate with a 95% confidence interval (CI) and a p-value for the likelihood ratio test. Kaplan-Meier curves were used for the graphic presentation.

The sensitivity analysis was performed considering only the patients from the Swedish registry that received HE-DMTs as initial therapy and those from the Czech registry that received LE-DMTs as initial therapy. An additional sensitivity analysis considered only patients who started in the years 2015 and 2016, since the proportion of the patients commencing HE-DMT in Sweden during these particular years was higher. For this comparison, the weights for the overall population comparison were used.

All evaluations were performed using R (version 4.2.1) (R Core Team 2022) and the dplyr, readxl, psych, XLConnect, Hmisc, tableone and survminer packages.

3. Results

3.1. Data description

In total, 3487 patients from the Czech registry whose data was exported in December 2021, and 2923 patients from the Swedish registry whose data was exported in March 2022 were included in the study. Out of all the patients included, 3327 of those from the Czech registry (95.41%) and 1771 of those from the Swedish registry (60.59%) had initiated their treatment with LE-DMT. The remaining patients had received HE-DMT as initial therapy.

The analysis included 2991 patients from the Czech registry and 1529 patients from the Swedish registry for whom the weights were calculated. The patients differed in age and duration of the disease, with those from the Swedish registry having a duration of disease that was more than one year longer at baseline. ARR prior to DMT initiation was almost twice as high in patients from the Czech registry (1.08 vs. 0.54). The patients were followed in average for 6.64 years in the Czech Republic, and for 5.9 years in Sweden (Table 1).

The HE-DMT initiation strategy was dominant in the Swedish registry (41.99%) compared to the Czech registry (3.81%).

The sensitivity analysis included 642 patients that received HE-DMT as initial therapy in Sweden and 2877 patients that received LE-DMTs as initial therapy in the Czech Republic (Table 2). The differences between the two groups were more pronounced than in the comparison of all patients included in the study. The groups differed mainly in age (mean 35.49 years and 37.04 years for LE-DMT and HE-DMT, respectively) and duration of the disease (mean 2.46 years and 4.46 years for LE-DMT and HE-DMT, respectively). The number of patients starting with HE-DMT in Sweden increased over the years (102 in 2013, 146 in 2014, 174 in 2015, and 220 in 2016). The proportion of patients for whom the escalation strategy was used in the Czech registry remained stable

Table 1
Baseline characteristics of the patients in the Czech and Swedish national registries. Only patients for whom weight values were available were included in the analysis.

		All analyzed patients			
		CZE	SWE	p-value	SDif
N		2991	1529		
Age*, mean±SD, years		35.5 ± 9.05	36.92 ±9.86	<0.001	0.15
Disease duration*, mean±SD, years		2.63±4.93	3.87±6	<0.001	0.23
EDSS*	mean±SD	2.01±1.01	1.66±1.53	<0.001	0.27
	median (IQR)	2 (1)	1.5 (2.5)		
ARR 12 months prior baseline*, mean±SD		1.08±0.66	0.54±0.68	<0.001	0.8
ARR 24 months prior baseline, mean±SD		0.62±0.38	0.33±0.38	<0.001	0.75
Follow-up, mean±SD, years		6.64±1.31	5.9 ± 1.67	<0.001	0.49
Annualized number of follow-up visits, mean±SD		3.24±0.87	1.37±0.51	<0.001	2.62
Gender*	F	2103 (70.31%)	1040 (68.02%)	0.113	0.05
	M	888 (29.69%)	489 (31.98%)		
Baseline year	2013	673 (22.5%)	336 (21.98%)	0.672	0.04
	2014	728 (24.34%)	398 (26.03%)		
	2015	800 (26.75%)	400 (26.16%)		
	2016	790 (26.41%)	395 (25.83%)		
DMT group	Low-moderate	2877 (96.19%)	887 (58.01%)	<0.001	1.02
	Moderate-high	114 (3.81%)	642 (41.99%)		
DMT	Dimethyl fumarate	35 (1.17%)	348 (22.76%)		
	Glatiramer acetate	822 (27.48%)	63 (4.12%)		
	Interferon beta-1a	1453 (48.58%)	302 (19.75%)		
	Interferon beta-1b	431 (14.41%)	93 (6.08%)		
	Pegylated interferon beta-1a	0 (0%)	45 (2.94%)		
	Teriflunomide	136 (4.55%)	36 (2.35%)		
	Alemtuzumab	1 (0.03%)	10 (0.65%)		
	Fingolimod	50 (1.67%)	61 (3.99%)		
	Natalizumab	36 (1.2%)	170 (11.12%)		
	Ocrelizumab	19 (0.64%)	2 (0.13%)		
	Ponesimod	2 (0.07%)	0 (0%)		
	Rituximab	6 (0.2%)	399 (26.1%)		

* Variables used in the propensity score model, hence exactly balanced between the CZE and SWE during the analysis.

Table 2
Baseline characteristics of patients who initiated low-moderate DMT in the Czech registry (LE-DMT CZE) and moderate-high DMT in the Swedish registry (HE-DMT SWE).

		Analyzed patients			
		LE-DMT (CZE)	HE-DMT (SWE)	p-value	SDif
N		2877	642		
Age*, mean±SD, years		35.49±9.06	37.04±10.3	<0.001	0.16
Disease duration*, mean ±SD, years		2.46±4.78	4.46±6.58	<0.001	0.35
EDSS*	mean±SD	1.97±0.97	2.07±1.72	0.127	0.08
	median (IQR)	2 (1)	2 (2)		
ARR 12 months prior baseline*, mean±SD		1.08±0.64	0.57±0.72	<0.001	0.76
ARR 24 months prior baseline, mean±SD		0.62±0.37	0.33±0.4	<0.001	0.74
Follow-up, mean±SD, years		6.64±1.32	5.63±1.66	<0.001	0.67
Annualized number of follow-up visits, mean ±SD		3.24±0.87	1.39±0.5	<0.001	2.62
Gender*	F	2028 (70.49%)	419 (65.26%)	0.009	0.11
	M	849 (29.51%)	223 (34.74%)		
Baseline year	2013	656 (22.8%)	102 (15.89%)	<0.001	0.22
	2014	689 (23.95%)	146 (22.74%)		
	2015	780 (27.11%)	174 (27.1%)		
	2016	752 (26.14%)	220 (34.27%)		

* Variables used in the propensity score model, hence exactly balanced between the CZE and SWE during the analysis.

during the entire period of the study.

3.2. Confirmed disability worsening

When the countries were compared in terms of CDW outcomes, patients from the Swedish registry showed slightly better results, mainly during longer follow-up. However, the 11% reduction (HR 0.89, 95% CI 0.77 to 1.03) in the probability of CDW with respect to patients from the Czech registry was not significant (p-value 0.2764) as shown in Fig. 1. Sensitivity analysis comparing only patients on HE-DMT and LE-DMT highlighted the trends (HR 0.81, 95% CI 0.66 to 0.99). However, the early crossing of the curves might have prevented the p-value from becoming significant.

A secondary sensitivity analysis that considered only patients with baseline in the years 2015 and 2016 showed an even more pronounced differences between patients from each registry. Patients from the Swedish registry were associated with a 23% reduction in the probability of CDW relative to patients from the Czech registry (p-value 0.0946, HR 0.77, 95% CI 0.62 to 0.96; Supplementary Figure 1)

3.3. Time to relapse and annualized relapse rate

The risk of relapse was significantly reduced by 66% in patients from the Swedish registry (p-value <0.001, HR 0.34, 95% CI 0.3 to 0.39; Fig. 1) relative to patients from the Czech registry. This was supported by the results of the sensitivity analysis of HE-DMTs vs LE-DMTs, which revealed a 83% reduction in the risk of relapse for patients receiving HE-DMTs as initial therapy (p-value <0.001, HR 0.17, 95% CI 0.13 to 0.21).

The average ARR for patients in the Czech registry was 0.199 with 0.266 SD, whereas the value was considerably lower for patients in the Swedish registry (mean 0.056, SD 0.141). When the results in patients on HE-DMT and LE-DMT alone were compared, the difference was even more evident (mean 0.208 and 0.268 SD in Czech registry patients receiving LE-DMT as initial therapy versus 0.033 and 0.135 SD in Swedish registry patients receiving HE-DMT as initial therapy).

3.4. Time to treatment switch

Patients from the Swedish registry were switched to DMT with a different mechanism of action sooner than those from the Czech registry (p-value <0.001, HR 1.43, 95% CI 1.31 to 1.58; Fig. 1). However, this was not the case when only those patients receiving HE-DMT versus LE-DMT as initial therapy were considered. In this sensitivity analysis, the trend was the opposite: patients from the Czech registry switched DMTs earlier (p-value <0.001, HR 0.46, 95% CI 0.39 to 0.55). The median time to treatment switch was 6.34 years for patients with LE-DMT in the Czech registry, and it was not reached for patients with HE-DMT in Sweden.

Most patients from the Czech registry (54%) were switched due to the lack of efficacy of the treatment (see Supplementary Table 1). The second main reason for treatment switch in patients from the Czech registry was the presence of side effects (28.84%). As almost all patients from the Czech registry received LE-DMT as initial treatment, the sensitivity analysis provided similar results. The main reason for treatment switch in patients from the Swedish registry was also a lack of efficacy (37.82%), followed by the presence of side effects (34.85%). However, when only patients from the Swedish registry that received HE-DMT were considered, the main reason for the discontinuation of treatment was another reason (52.6%), followed by lack of efficacy (23.77%) and side effects (14.96%).

3.5. Confirmed disability improvement

In the Czech Republic, a minimum of patients experienced CDI as shown in Fig. 1. In contrast, in the Swedish registry patients significantly improved three times more often (p-value <0.001, HR 3.04, 95% CI 2.37 to 3.9). This strong trend was confirmed by the sensitivity analysis as well (p-value <0.001, HR 2.76, 95% CI 2.05 to 3.72).

4. Discussion

By using data from the Czech and Swedish national MS registries of RRMS patients starting their first DMT between the years 2013 and 2016, we aimed to confirm the results of a previous comparison of the effect of different treatment strategies on long-term disability outcomes (Spelman et al., 2021). The objective of the previous study was to investigate whether receiving HE-DMT as initial therapy results in a better long-term disability outcome compared to starting patient treatment with LE-DMT (despite an eventual switch to HE-DMT later on). The previous study found a significantly lower risk of CDW in a Swedish cohort compared to that in a Danish cohort, where much smaller percentage of RRMS patients receive HE-DMT as initial treatment. As the treatment strategy preference in the Czech Republic was similar to that in Denmark, we repeated the comparison against the Swedish cohort, but this time with the Czech RRMS population replacing the Danish population. In the Czech Republic, only 4.59% of RRMS patients initiated the treatment directly with HE-DMT within the years 2013 and 2016, whereas in Sweden this strategy was substantially more frequent in the RRMS population (39.41%).

Despite the similarities between the Swedish and Czech RRMS populations, the patients differed slightly but significantly in several baseline characteristics, which may be related to differences in the timing of diagnosis. To minimize potential biases deriving from these differences, the outcomes were balanced using propensity score overlap weights. For the propensity score model, age, gender, duration of the disease, baseline EDSS and ARR calculated 12 months before the initiation of the first DMT were balanced. The model differed from the previous study in several variables. ARR values from 24 months prior to the study baseline were not considered, as they were highly correlated with the values recorded 12 months prior to the study baseline. The number of follow-up visits differed between the registries but was also not considered for the propensity score model. This variable differed between the registries

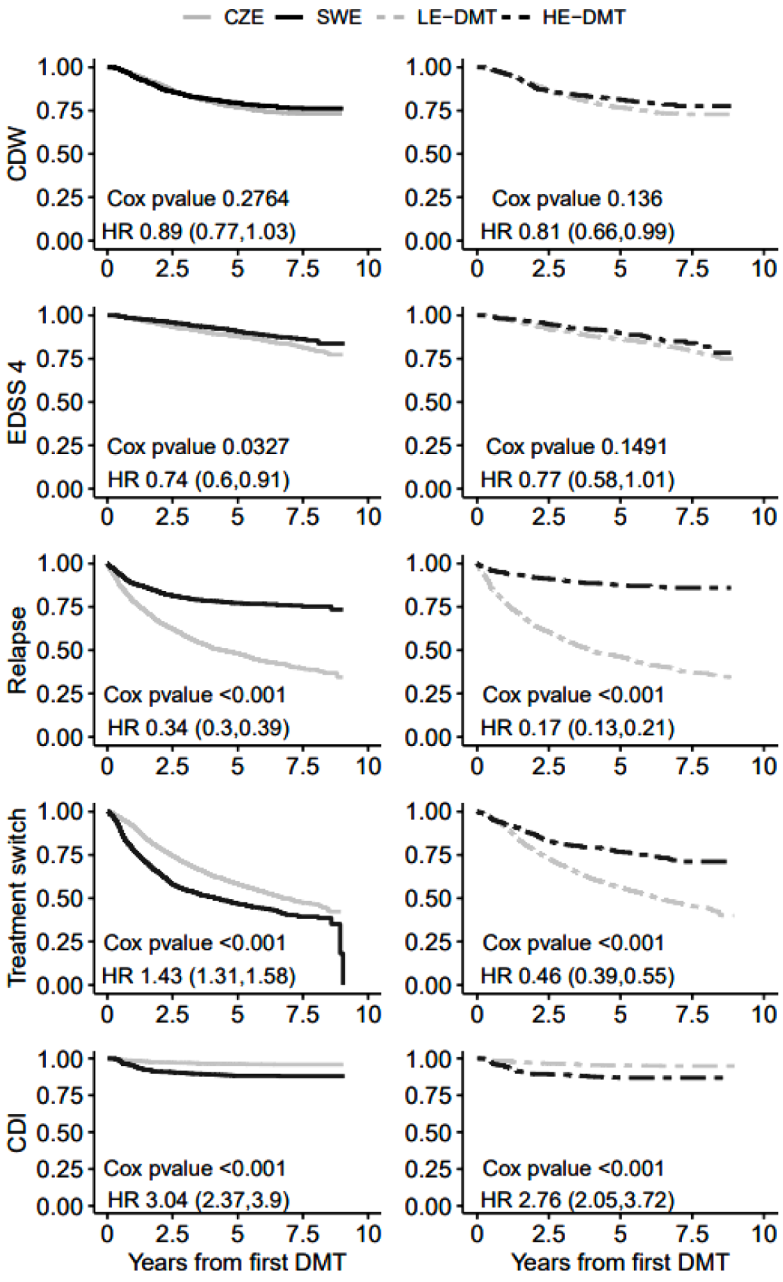

Fig. 1. Kaplan-Meier curves describing the proportion of patients who: remained CDW free (CDW), remained below EDSS 4 (EDSS 4), did not experience any relapse (Relapse), stayed on DMT with same mode of action (Treatment switch) and remained without CDI (CDI). Solid curves represent comparisons between entire registries (CZE vs. SWE), dashed curves represent comparisons between patients from the Swedish registry on HE-DMT (HE-DMT) and patients from the Czech registry on LE-DMT (LE-DMT).

consistently (patients from the Swedish registry had a lower frequency of visits in general), and therefore it was considered as too deterministic and not appropriate to be incorporated in the modeling. Neuroimaging data is not included in the Czech registry to the same extent as in the Swedish registry, preventing us from analyzing magnetic resonance imaging (MRI) measures in the present study. The overlap weight method was selected because it avoids the multiplication of patients in the analysis, is very consistent, and assures equality of the mean values between the cohorts of selected variables.

In contrast to the previous comparison between the Swedish and Danish cohorts (Spelman et al., 2021), the primary outcome (CDW) did not show a significant difference in favor of the Swedish cohort (HR 0.89, p-value 0.2764). Even when only the patients receiving HE-DMTs as initial therapy in Sweden were considered, the difference remained non-significant (HR 0.81, p-value 0.136). However, in the second case, the insignificance might be caused by the early crossing of the survival curves: the curves diverged after the first 2.5 years of follow-up, and the prognosis was more favorable for patients with HE-DMT from the Swedish registry.

In contrast to what was observed for the primary outcome, all the remaining time-to-event outcomes considered showed significant differences between the registries. For patients from the Swedish registry, the risk of reaching EDSS 4 was reduced by 26% (HR 0.74, p-value 0.0327), the risk of relapse was reduced by 66% (HR 0.34, p-value <0.001) and the probability of CDI was three times higher (HR 3.04, p-value <0.001). Thus, it is reasonable to ask why such a significant reduction in the risk of relapse did not translate into a change in the long-term outcome of CDW. Our hypothesis is that the evaluation methods of EDSS might differ between the countries, as EDSS cannot be considered a hard endpoint, especially for the lower part of the scale (Noseworthy et al., 1990; Amato et al., 1988). This is supported by the fact that hard outcomes such as time to EDSS 4, which is characterized by restricted walking ability, and time to relapse were significantly better for patients from the Swedish registry. Moreover, as previously mentioned, different variables were used for weighting between the present and the previous study due to reasons related to data

availability. For instance, the MRI status of the patients could not be balanced between the Swedish and Czech cohorts, which could have affected the results for the primary outcome.

Treatment switch has particular characteristics in different countries, not just in terms of the initial choice of DMT but also in the approach adopted for later escalation. The patients in Sweden were switched much sooner than in the Czech Republic (HR 1.43, p-value <0.001). This would suggest that patients starting on LE-DMTs in Sweden were quickly escalated to HE-DMTs, which seems to be confirmed by the sensitivity analysis. According to the sensitivity analysis, when only patients from Sweden receiving HE-DMT as first therapy and patients from the Czech Republic receiving LE-DMT as first therapy are considered, the treatment switch trends were the opposite compared to those in the main analysis (HR 0.46, p-value <0.001). After eight years of follow-up, 68% of patients from the Swedish registry on HE-DMT were still without the need for a switch, compared to only 40% of patients from the Czech registry on LE-DMT. This means that patients on HE-DMT stayed on therapy much longer compared to the rest of the patients. The higher efficacy and good tolerance demonstrated by HE-DMT were also confirmed by the analysis of the reasons provided for the switch of treatment: more than half of the patients (54%) in the Czech registry were switched due to the lack of efficacy of the treatment, whereas in Sweden only 37.82% of the patients mentioned this as a reason. The possibility that an early switch of HE-DMTs may increase the incidence of side effects was not confirmed, as only 14.96% of patients receiving HE-DMT switched therapies due to side effects.

The primary limitation of this study revolves around the baseline disparities observed between the two national study populations. Although expected to be similar due to similar ethnicity, diagnostics and general clinical practice, some differences were apparent, including variances in disease duration, baseline EDSS scores, and particularly ARR measurements taken 12 months prior to baseline. To address these baseline differences, we employed propensity score weighting to moderate the imbalances. This method assured to balance the baseline characteristics between the two cohorts. Nevertheless, it is important to note that no statistical method can guarantee complete elimination of bias in the analysis, as this is a real-world evidence study.

5. Conclusion

The analysis of the Czech and Swedish MS registries confirmed a better prognosis for patients in Sweden, where a significant proportion of patients received HE-DMTs as initial therapy. Despite the high frequency of early treatment switches in patients that received LE-DMT in both countries, the prognosis of patients in Sweden was better in terms of outcomes including relapses, time to EDSS 4 and others. As the highest proportion of patients switched from LE-DMT early because of the lack of efficacy, it is highly questionable whether LE-DMT is indeed the best initial treatment choice for RRMS patients.

CRediT authorship contribution statement

Tereza Hrnciarova: Conceptualization, Methodology, Software, Formal analysis, Validation, Data Curation, Visualization, Writing – original draft. Jiri Drahota: Conceptualization, Data Curation, Validation, Writing – review & editing. Tim Spelman, Jan Hillert, Jan Lycke: Conceptualization, Methodology, Data Curation, Investigation, Writing – review & editing. Eva Kubala Havrdova, Eva Recmanova, Jana Adamkova, Jan Mares, Jana Libertinova, Zbysek Pavelek, Pavel Hradilek, Radek Ampapa, Ivana Stetkarova, Marek Peterka, Alena Martinkova, Pavel Stourac, Marketa Grunermelova, Marta Vachova, Michal Dufek: Investigation, Writing – review & editing. Dana Horakova: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

T. Hrnciarova has nothing to disclose. J. Drahota has nothing to disclose. T. Spelman received compensation from serving on scientific advisory boards and steering comittees from Biogen and consultancy fees from Hartmann and Abbvie. J. Hillert received honoraria for serving on advisory boards for Biogen, Bristol-Myers-Squibb/Celgene, Janssen, Merck KGaA, Sandoz and Sanofi-Genzyme and speaker...s fees from Biogen, Janssen, Novartis, Merck, Teva, Sandoz and Sanofi-Genzyme. He has served as P.I. for projects sponsored by, or received unrestricted research support from, Biogen, Bristol-MyersSquibb/Celgene, Janssen, Merck KGaA, Novartis, Roche, and Sanofi-Genzyme. His MS research is funded by the Swedish Research Council and the Swedish Brain foundation. J. Lycke has received travel support and/or lecture honoraria and has served on scientific advisory boards for Alexion, Almirall, Biogen, Bristol Myers Squibb, Celgene, Janssen, Merck, Novartis, Roche and Sanofi; and has received unconditional research grants from Biogen and Novartis, and financial support from Sanofi for an investigator-initiated study. E. Kubala Havrdova has received honoraria/research support from Biogen, Merck Serono, Novartis, Roche, and Teva; has served as a member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, and Sanofi Genzyme; has been supported by the Czech Ministry of Education project Cooperatio LF1, research area Neuroscience, and the project National Institute for Neurological Research (Programme EXCELES, ID project No LX22NPO5107) funded by the European Union-Next Generation EU. E. Recmanova has nothing to disclose. J. Adamkova has nothing to disclose. J. Mares has nothing to disclose. J. Libertinova reported receiving grants, personal fees and funding for travel from Merck, Roche, Novartis, Biogen Inc, Sanofi Genzyme. Z. Pavelek reports personal fees from Biogen, Eli Lilly, Genzyme, Merck Serono, Novartis, Pfizer, Roche, and Teva Pharma. P. Hradilek received speakers honoraria and travel compensations from Biogen, Merck, Teva, Sanofi, Roche, Novartis and Janssen Cilag. R. Ampapa received conference travel support from Roche, Sanofi, Biogen and Merck and has participated in clinical trials by Biogen, Novartis, Sanofi, Merck and Roche. I. Stetkarova received compensation for travel and speaker honoraria from Biogen Idec, Merck, and Roche. M. Peterka has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Merck, Novartis, Biogen, Sanofi-Genzyme, Jansse-Cilag, Teva, Roche. A. Martinkova has nothing to disclose. P. Stourac has nothing to disclose. M. Grunermelova has nothing to disclose. M. Vachova received compensation for travel, conference fees, consulting fees and speaker honoraria from Biogen, Lundbeck, Merck, Novartis, Roche, Sanofi, and Teva. M. Dufek has nothing to disclose. D. Horakova was supported by the Charles University: Cooperatio Program in Neuroscience, by the project National Institute for Neurological Research (Programme EXCELES, ID Project No. LX22NPO5107) - Funded by the European Union Next Generation EU, and by General University Hospital in Prague project MH CZ-DRO-VFN64165. She also received compensation for travel, speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, and Teva, as well as support for research activities from Biogen Idec.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.104803.

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