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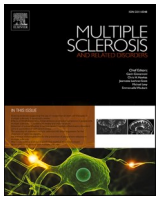

Does initial high efficacy therapy in multiple sclerosis surpass escalation treatment strategy? A comparison of patients with relapsing-remitting multiple sclerosis in the Czech and Swedish national multiple sclerosis registries

Tereza Hrnciarova [a,b], Jiri Drahota [a,c], Tim Spelman [d], Jan Hillert [d], Jan Lycke [e], Eva Kubala Havrdova [a], Eva Recmanova [f], Jana Adamkova [g], Jan Mares [h], Jana Libertinova [i], Zbysek Pavelek [j], Pavel Hradilek [k], Radek Ampapa [l], Ivana Stetkarova [m], Marek Peterka [n], Alena Martinkova [o], Pavel Stourac [p], Marketa Grunermelova [q], Marta Vachova [a,r], Michal Dufek [s], Dana Horakova [a,*]

[a] *Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic*
[b] *Department of Epidemiology and Biostatistics, Third Faculty of Medicine, Charles University in Prague, Prague, Czech Republic*
[c] *IMPULS Endowment Fund, Prague, Czech Republic*
[d] *Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden*
[e] *Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*
[f] *Bata Regional Hospital, Zlín, Czech Republic*
[g] *Department of Neurology, Hospital České Budějovice, České Budějovice, Czech Republic*
[h] *Department of Neurology and Centre of Clinical Neuroscience, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic*
[i] *Department of Neurology, Second Faculty of Medicine and Motol University Hospital, Charles University in Prague, Prague, Czech Republic*
[j] *Department of Neurology, Faculty of Medicine and University Hospital Hradec Králové, Charles University in Prague, Hradec Králové, Czech Republic*
[k] *Department of Clinical Neuroscience, Medical Faculty, Ostrava University and Department of Neurology, University Hospital, Ostrava, Czech Republic*
[l] *Department of Neurology, Hospital Jihlava, Jihlava, Czech Republic*
[m] *Department of Neurology, Third Faculty of Medicine, Charles University in Prague and University Hospital Kralovske Vinohrady, Prague, Czech Republic*
[n] *Department of Neurology, Faculty of Medicine in Pilsen and University Hospital Pilsen, Charles University in Prague, Pilsen, Czech Republic*
[o] *Department of Neurology, Hospital Pardubice, Pardubice, Czech Republic*
[p] *Department of Neurology, University Hospital Brno, Brno, Czech Republic*
[q] *Department of Neurology, Thomayer Hospital, Prague, Czech Republic*
[r] *Department of Neurology, KZ a.s., Hospital Teplice, Teplice, Czech Republic*
[s] *First Department of Neurology, Masaryk University, St. Anne's University Hospital, Brno, Czech Republic*

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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,

* Corresponding author.
E-mail address: dana.horakova@vfn.cz (D. Horakova).

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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

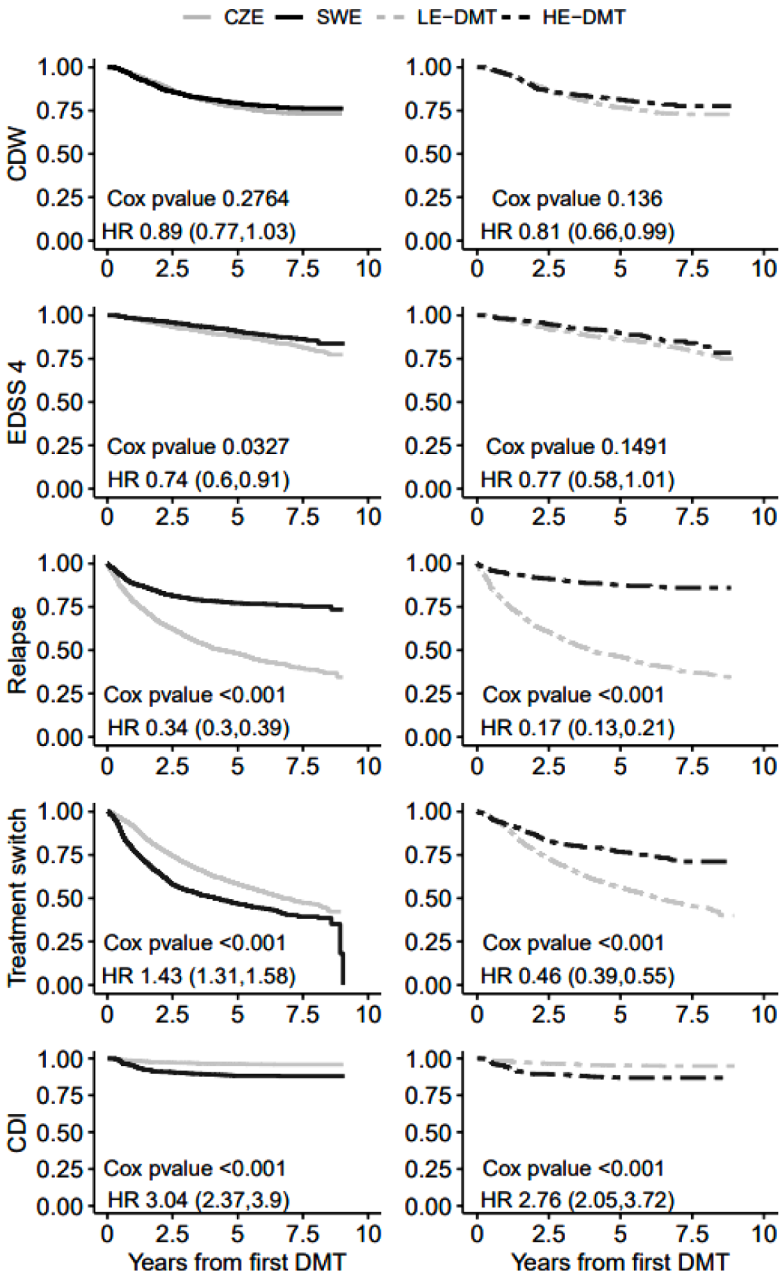

Fig. 1. Kaplan-Meier curves describing the proportion of patients who: remained CDW free (CDW), remained below EDSS 4 (EDSS 4), did not experience any relapse (Relapse), stayed on DMT with same mode of action (Treatment switch) and remained without CDI (CDI). Solid curves represent comparisons between 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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Declaration of Competing Interest

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

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