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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;.

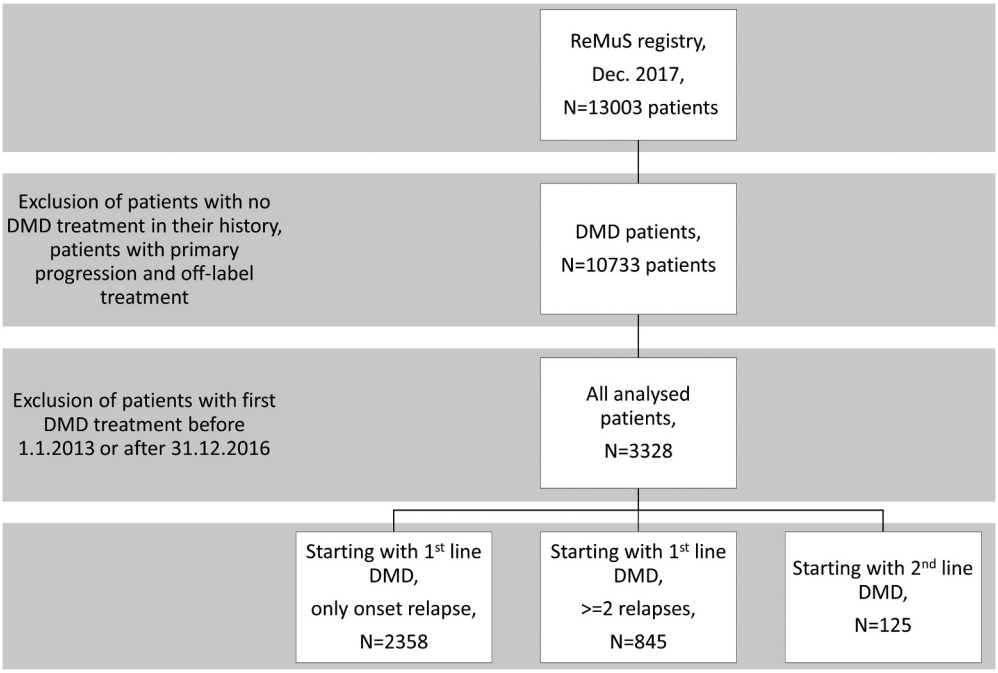

Fig. 1. Flowchart of patient disposition.

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;.

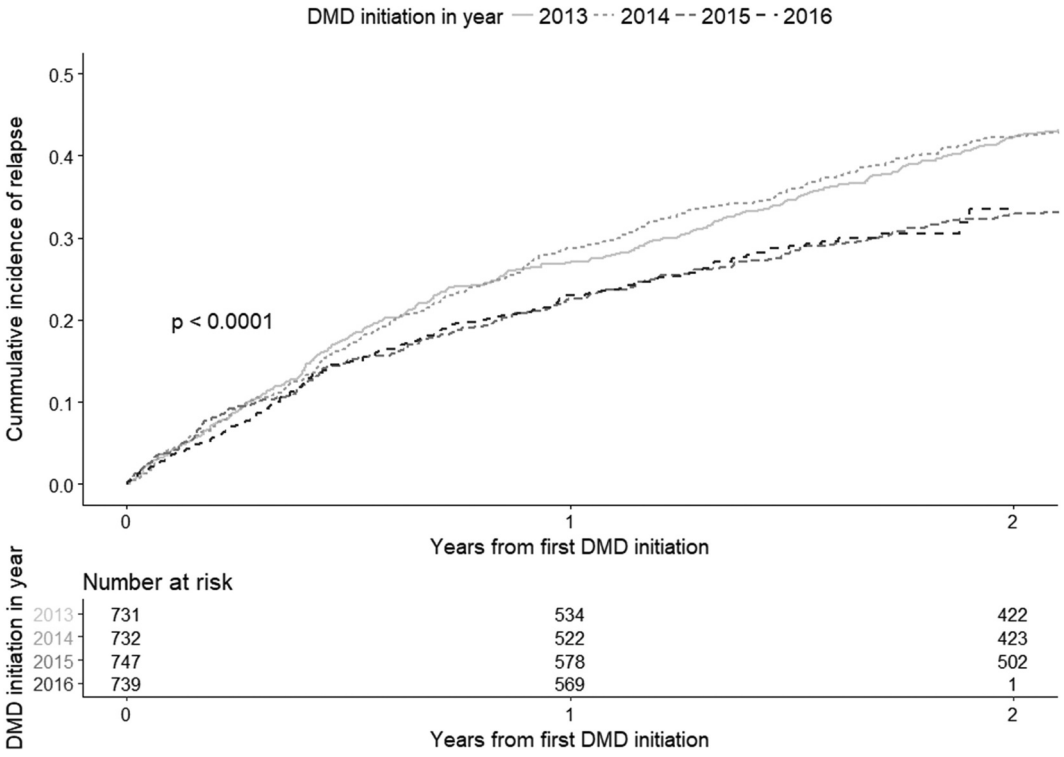

Fig. 2. Kaplan-Meier curves for time to first relapse after DMD initiation for cohorts of first-line patients starting in different years, p-value from log rank test is presented.

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

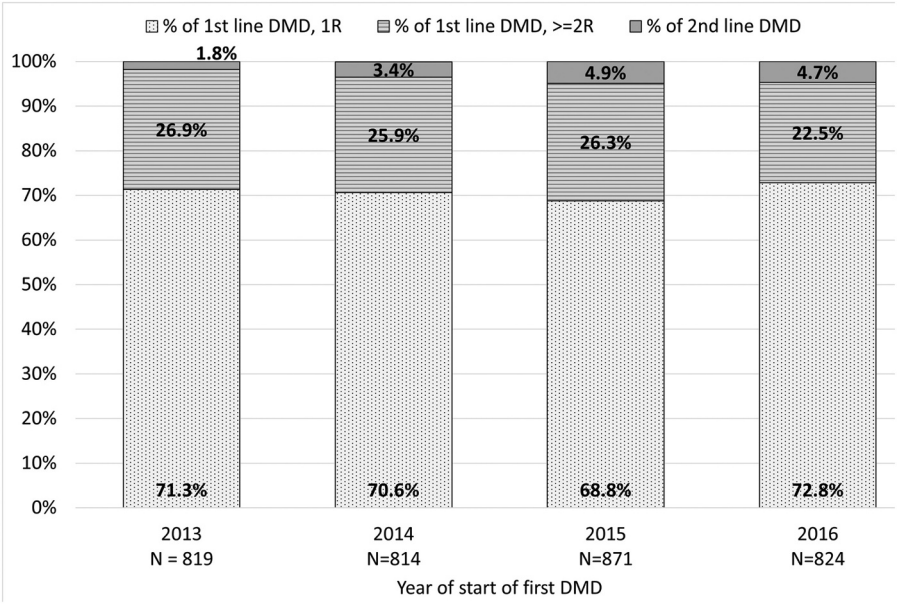

Fig. 3. Number of patients who started their first treatment in years 2013–2016 and their distribution in each year based on the type of first DMD and number of previous relapses (R), first-line DMDs include interferons, glatiramer acetate, and teriflunomide, second-line DMDs include dimethyl fumarate,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