The Czech National MS Registry (ReMuS): Data trends in multiple sclerosis patients whose first disease-modifying therapies were initiated from 2013 to 2021

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Aims. Multiple sclerosis treatment strategies are changing in the Czech Republic. According to data from 2013–2021, the proportion of patients starting high-efficacy disease-modifying therapies is increasing. In this survey, we describe the actual data trends in multiple sclerosis (MS) patients beginning their first disease-modifying therapies (DMTs) from 2013 to 2021. The secondary objective was to present the history, data collection, and scientific potential of the Czech National MS registry (ReMuS).

Methods. First, using descriptive statistics, we analysed the data for patients starting their first DMTs, either platform (including dimethyl fumarate) or high-efficacy DMTs (HE-DMTs), for each successive year. Second, a detailed description of the history, data collection, completeness, quality optimising procedures, and legal policies of ReMuS is provided.

Results. Based on the dataset from December 31, 2021, the total number of monitored patients with MS in ReMuS increased from 9,019 in 2013 (referred from 7 of 15 MS centres) to 12,940 in 2016 (referred from all 15 Czech MS centres) to 17,478 in 2021. In these years, the percentage of patients treated with DMTs in the registry ranged from 76 to 83%, but the proportion of patients treated with HE-DMTs changed from 16.2% in 2013 to 37.1% in 2021. During the follow-up period, a total of 8,491 treatment-naive patients received DMTs. The proportion of patients (all MS phenotypes) starting HE-DMTs increased from 2.1% in 2013 to 18.5% in 2021.

Conclusion. Patient registries, including ReMuS, provide an essential quality data source, especially in light of the increasing percentage of patients on HE-DMTs. Although early initiation of HE-DMT can provide considerable benefits, it also carries greater potential risks. Consistent long-term follow-up of patients in real-world clinical practice, which only registries allow, is therefore crucial to evaluate the efficacy and safety of therapeutic strategies, for epidemiological research and to assist decision making by healthcare providers and regulatory bodies.

Key words: multiple sclerosis, disease-modifying therapy, high-efficacy therapy, platform therapy, treatment initiation, real-world data, registry, epidemiology

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INTRODUCTION

Multiple sclerosis (MS) is a chronic neurological disease with a mean age of diagnosis around 30 years, therefore presenting at a highly productive stage of life. In addition, the prevalence of the disease continues to rise. The estimated number of people with MS worldwide has increased to 2.8 million in 2020, 30% higher than in 2013 (ref.[1]). As such, MS has a significant impact on both affected individuals and society.

Fortunately, the arsenal of treatment options is growing, with more than 15 different disease-modifying therapies (DMTs) with various efficacy and safety profiles available to date. However, the heterogeneity of MS courses, including treatment responses, remains incompletely understood, and an individually tailored approach remains complicated. Clinical trials usually provide short-term information about therapies under controlled conditions, often different from those in clinical practice. Thus, the effectiveness, safety, and tolerability of DMTs tested in clinical trials and then applied in a clinical population with a comorbidity burden, and other special characteristics, are uncertain[2].

Registries are powerful data sources with the potential to fill these knowledge gaps and provide high-quality long-term epidemiological data about real-world conditions. Both international and national registries are important, especially given differences in genetic disposition and environmental or socioeconomic factors. Furthermore, many countries still do not reimburse all DMTs, or they restrict the order in which therapies can be administered. This is proving problematic in light of the growing evidence of significant benefits from early initiation of highly effective therapies (HE-DMTs) (ref.[3-10]). Registry data can show national regulators and institutions responsible for reimbursement criteria that limiting access to some DMTs may be less cost-effective in the long-term.

In this paper, we have two aims. First, as mentioned, the type of DMT and its early initiation is essential for the patient's prognosis. Therefore, a primary aim was to describe the trend in the characteristics of patients initiating DMTs, either platform therapies (P-DMTs) or HE-DMTs. Second, we present the Czech National Multiple Sclerosis Registry (ReMuS), specifically its history, data collection, completeness, quality optimising procedures and legal policies.

METHODS

Patients in ReMuS

This paper describes the characteristics of patients in ReMuS based on the most recent data exported as of December 31, 2021. First, the total number of patients with data in the registry and the total number of alive and monitored patients with clinically isolated syndrome (CIS) or definite MS included in the registry were evaluated at the end of each year. We focused in detail on the category of DMT used (P-DMT or HE-DMT), DMT discontinuation, and switches (Table 1). Second, we wanted to describe patients who started their first DMT each year between 2013 and 2021. This period provides us with the highest quality data, as it was collected prospectively, back-traced, and repeatedly quality-controlled since 2013 (Table 2).

Stratification of patients was based on the type of their first DMT, whether it was a P-DMT (interferons, glatiramer acetate, teriflunomide or dimethyl fumarate) or a HE-DMT (alemtuzumab, cladribine, S1P modulators, anti-CD20 therapies, or natalizumab), and by the Czech reimbursement criteria. As in several other European countries, access to DMTs is defined by two conditions. First, the rules under which the DMT was registered in the European Union and second, the reimbursement crite-

Table 1. Description of patients with data in ReMuS as of 31.12. each year.

No. (%)/year	2013	2014	2015	2016	2017	2018	2019	2020	2021
MS centres	7	12	13	15	15	15	15	15	15
Patients	9,694	11,156	12,455	13,912	14,933	16,144	17,298	18,363	19,174
Alive and monitored MS patients	9,019	10,401	11,615	12,940	13,872	14,940	15,873	16,767	17,478
Alive and monitored MS patients on DMTs	7,496 (82.8)	8,234 (79.2)	9,090 (78.3)	9,898 (76.5)	10,607 (76.5)	11,408 (76.4)	12,227 (77.4)	13,097 (78.1)	13,659 (78.2)
Patients on P-DMTs	6,260 (83.8)	6,682 (81.2)	7,281 (80.1)	7,780 (78.6)	8,121 (76.6)	8,444 (74.0)	8,556 (69.7)	8,631 (65.9)	8,591 (62.9)
Patients on HE-DMTs	1,209 (16.2)	1,552 (18.9)	1,809 (19.9)	2,118 (21.4)	2,486 (23.4)	2,964 (26.0)	3,721 (30.3)	4,466 (34.1)	5,068 (37.1)
Alive and monitored MS patients newly initiating DMTs[1]	1,811 (20.1)	1,891 (18.2)	2,505 (21.6)	2,406 (18.6)	2,513 (18.1)	2,578 (17.3)	2,784 (17.5)	2,498 (14.9)	2,086 (11.9)
Patients on the same newly initiated DMT after one year	1,538 (84.9)	1,600 (84.6)	2,091 (83.5)	1,965 (81.7)	2,037 (81.1)	2,059 (79.9)	2,340 (84.1)	2,113 (84.6)	X
Alive and monitored MS patients discontinuing DMTs[2]	1,063 (11.8)	1,127 (10.8)	1,658 (14.3)	1,595 (12.3)	1,806 (13.0)	1,793 (12.0)	1,922 (12.1)	1,662 (9.9)	1,514 (8.7)

1: does not take into account any previous treatment – contains naive patients as well as pre-treated (e.g. switches); 2: does not take into account any following treatment – contains switches; MS, multiple sclerosis; ReMuS, the Czech national registry of patients with multiple sclerosis; DMT, disease-modifying therapy; P-DMT, platform disease-modifying therapy (interferons, glatiramer acetate, teriflunomide, dimethyl fumarate); HE-DMT, high-efficacy disease-modifying therapy (alemtuzumab, cladribine, S1P modulators, anti-CD20 therapies, natalizumab).

Table 2. Description of alive and monitored treatment-naive patients with MS in ReMuS as of 31.12. each year.

	2013	2014	2015	2016	2017	2018	2019	2020	2021
No. of treatment-naive patients (%)	888	930	999	991	970	1024	1021	967	701
Patients initiating P-DMTs after one relapse	614 (69.1)	618 (66.5)	662 (66.3)	663 (66.9)	659 (67.9)	617 (60.3)	598 (58.6)	612 (63.3)	441 (62.9)
Patients initiating P-DMTs after more than one relapse	255 (28.7)	250 (26.9)	302 (30.2)	273 (27.6)	275 (28.4)	278 (27.2)	267 (26.2)	172 (17.8)	130 (18.5)
Patients initiating HE-DMTs	19 (2.1)	62 (6.7)	35 (3.5)	55 (5.6)	36 (3.7)	129 (12.6)	156 (15.3)	183 (18.9)	130 (18.5)
Age at MS onset; mean (SD)	32.3 (9.6)	32.8 (10.0)	33.1 (9.9)	33.0 (9.8)	33.3 (10.4)	33.4 (9.8)	34.8 (10.4)	35.2 (10.7)	34.2 (10.9)
Patients initiating P-DMTs after one relapse	32.9 (9.7)	33.6 (9.9)	33.9 (9.9)	33.5 (9.9)	34.4 (10.4)	33.9 (9.9)	34.8 (10.0)	34.3 (10.2)	33.7 (10.1)
Patients initiating P-DMTs after more than one relapse	31.2 (9.5)	31.7 (10.4)	31.6 (9.7)	32.3 (9.4)	31.6 (10.3)	32.2 (9.0)	32.8 (10.3)	34.0 (9.9)	33.4 (10.4)
Patients initiating HE-DMTs	27.1 (8.6)	29.6 (8.1)	30.5 (9.3)	31.3 (9.4)	27.7 (7.8)	33.5 (10.8)	38.0 (11.5)	39.3 (11.8)	36.6 (13.3)
Gender (% of males)	271 (30.5)	259 (27.9)	290 (29.0)	302 (30.5)	260 (26.8)	318 (31.1)	335 (32.8)	315 (32.6)	228 (32.5)
Patients initiating P-DMTs after one relapse	194 (31.6)	180 (29.1)	201 (30.4)	206 (31.1)	191 (29.0)	184 (29.8)	187 (31.3)	192 (31.4)	147 (33.3)
Patients initiating P-DMTs after more than one relapse	68 (26.7)	62 (24.8)	78 (25.8)	78 (28.6)	60 (21.8)	78 (28.1)	79 (29.6)	48 (27.9)	34 (26.2)
Patients initiating HE-DMTs	9 (47.4)	17 (27.4)	11 (31.4)	18 (32.7)	9 (25.0)	56 (43.4)	69 (44.2)	75 (41.0)	47 (36.2)
EDSS at the DMT initiation; mean (SD)	2.1 (1.1)	2.1 (1.1)	2.1 (1.1)	2.1 (1.1)	2.2 (1.1)	2.2 (1.2)	2.3 (1.3)	2.4 (1.3)	2.3 (1.3)
Patients initiating P-DMTs after one relapse	1.9 (1.0)	1.9 (0.9)	1.9 (1.0)	1.9 (0.9)	2.0 (1.0)	1.9 (0.9)	1.9 (0.9)	1.9 (0.9)	1.9 (0.85)
Patients initiating P-DMTs after more than one relapse	2.5 (1.1)	2.5 (1.0)	2.3 (1.1)	2.4 (1.1)	2.5 (1.1)	2.4 (1.1)	2.4 (1.2)	2.3 (1.04)	2.1 (1.03)
Patients initiating HE-DMTs	3.9 (1.4)	3.2 (1.5)	3.2 (1.7)	3.4 (1.4)	4.0 (1.8)	3.6 (1.6)	4.2 (1.4)	2.9 (1.4)	3.8 (1.5)
Time from MS onset to DMT; mean, y (SD)	2.6 (4.7)	2.9 (5.4)	2.9 (5.1)	2.8 (5.3)	2.6 (5.2)	3.3 (6.0)	3.0 (5.6)	2.4 (5.0)	2.7 (6.3)
Patients initiating P-DMTs after one relapse	1.3 (3.0)	1.0 (2.6)	1.0 (2.5)	1.3 (3.7)	0.9 (2.3)	0.8 (2.8)	0.7 (2.1)	0.6 (1.9)	0.5 (1.3)
Patients initiating P-DMTs after more than one relapse	5.3 (6.2)	6.5 (7.6)	6.5 (6.7)	5.5 (6.3)	6.0 (6.9)	6.1 (6.7)	6.2 (7.2)	4.9 (6.6)	5.1 (7.4)
Patients initiating HE-DMTs	9.4 (6.6)	7.4 (5.5)	6.2 (7.7)	7.8 (7.5)	9.3 (9.2)	9.2 (8.1)	6.5 (6.9)	5.9 (7.0)	7.7 (10.2)
Time from MS onset to DMT; median, y (IQR)	0.5 (0.3, 2.0)	0.5 (0.3, 2.4)	0.6 (0.3, 2.5)	0.5 (0.3, 2.0)	0.5 (0.3, 1.5)	0.5 (0.3, 2.8)	0.5 (0.3, 2.7)	0.5 (0.2, 1.6)	0.4 (0.2, 1.4)
Patients initiating P-DMTs after one relapse	0.4 (0.2, 0.7)	0.3 (0.2, 0.6)	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	0.3 (0.2, 0.6)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)	0.3 (0.2, 0.4)
Patients initiating P-DMTs after more than one relapse	2.3 (0.9, 8.1)	3.7 (1.0, 9.3)	4.5 (1.2, 9.9)	3.0 (0.9, 8.5)	3.0 (0.8, 9.9)	2.9 (0.7, 10.2)	3.0 (0.9, 9.6)	1.9 (0.6, 6.4)	1.8 (0.5, 6.3)
Patients initiating HE-DMTs	10.3 (3.8, 13.3)	6.1 (2.4, 11.7)	1.8 (0.6, 11.2)	4.5 (1.5, 11.9)	6.2 (2.0, 14.2)	7.0 (2.3, 14.0)	4.7 (1.5, 8.6)	3.2 (1.4, 7.6)	3.1 (0.7, 9.7)

MS, multiple sclerosis; ReMuS, the Czech national registry of patients with multiple sclerosis; P-DMT, platform disease-modifying therapy (interferons, glatiramer acetate, teriflunomide, dimethyl fumarate); HE-DMT, high-efficacy disease-modifying therapy (alemtuzumab, cladribine, S1P modulators, anti-CD20 therapies, natalizumab); EDSS, Expanded Disability Status Scale.

ria. These are usually stricter than the registration criteria for the European Union. P-DMTs, except for dimethyl fumarate, can be prescribed to newly diagnosed patients immediately after the first relapse. For prescribing HE-DMTs, at least two moderate relapses during the previous year were required. Fortunately, these rules are gradually changing, and the reimbursement criteria are slowly getting more flexible, also thanks to registry data.

We divided patients initiating DMTs into three groups: (1) patients who initiated P-DMTs after the first relapse (P-DMT 1R), (2) patients who initiated P-DMTs after more than one relapse (P-DMT 2+R), and (3) patients who initiated HE-DMTs. Variables included in our analysis were also the age at the onset of the disease, gender, EDSS score at the first-ever DMT, and time from the onset of the disease to the first DMT.

Statistical analysis

To summarise the characteristics of all MS patients in each year, as well as the characteristics of each group, we used descriptive statistics. Data analyses were performed in R version 4.0.4.

ReMuS, its history and network

ReMuS is operated by an independent organisation, the IMPULS Endowment Fund, in collaboration with the Section of Clinical Neuroimmunology and Liquorology, the Czech Neurological Society, and the Czech Medical Association of J. E. Purkyně (SCNIL) as an expert guarantor. The registry collects data on patients with MS (both treated with DMTs and, since 2015, also non-treated) and other neuroimmunological diseases (neuromyelitis optica spectrum disorder, myelin oligodendrocyte glycoprotein antibody-associated disease, etc.) from all 15 specialised MS centres in the Czech Republic. As prescribing DMTs is limited to these specialised centres, the representation of patients treated by these therapies in the registry is high, almost complete[11,12]. The Czech Republic has a population of about 10.7 million, with the MS population estimated to be around 22,000–25,000. ReMuS collects data from approximately 85% of these patients[11].

ReMuS was founded in 2013 by the IMPULS Endowment Fund (IMPULS), a not-for-profit foundation active since 2000, as an organisation supporting research and treatment of multiple sclerosis. Since ReMuS has been using iMed software developed within MSBase as a data collection tool since its inception, it is closely linked to the international MSBase database[13]. Thus with informed consent, it is possible to directly share pseudo-anonymised data with MSBase, an important feature for research. At the same time, ReMuS participates independently in other European and global research projects.

An example of such projects is their involvement in the Big MS Data Network (BMSD) (ref.[14]), whose other members are currently the Swedish, Danish, French, Italian, and MSBase registries. Another example is participation in the Research Collaboration Network (RCN) project, which aims to map the situation regarding the secondary progressive form of MS.

Data from the registry have also been used in several academic projects[15–19]. For example, data from real clinical practice have allowed a closer focus on pregnancy in MS (ref.[17]). In addition, the already established structure of the registry has allowed a rapid assessment of the effectiveness and safety of interventions against COVID-19 since the beginning of the pandemic[16,19].

Data collection

As mentioned, ReMuS collects data using the standardised software iMed. At the time of diagnosis, emphasis is placed on the retrospective determination of the onset of the disease, the nature and severity of the first symptoms, and the results of paraclinical diagnostic examinations (including the basic cerebrospinal fluid test and magnetic resonance imaging). It is important to note that an examination of cerebrospinal fluid is standard diagnostic procedure in the Czech Republic. During treatment, patients are monitored through clinical visits scheduled at regular intervals with the recording of demographic, clinical, and paraclinical data, including data on the individual functional subsystems of the Expanded Disability Status Scale (EDSS), DMT administration, pregnancy and breastfeeding[17], and severe and life-threatening adverse events. Relapses are recorded with their dates, severity, and treatment. Since March 2020, data on COVID-19, its symptoms, severity, prevention (including vaccination), and treatment have also been collected[16,19] (Table 3). Cognitive screening, the 25 foot walk test, a nine-hole peg test, information on comorbidities and adverse events, and a few other measures are organised in an optional dataset in which not all MS centres have participated yet.

Every six months (except for specific projects), all data is exported from each MS centre. The data then undergoes a multi-level quality control process (more than 100 pre-programmed checks), and quality reports are sent back to each centre to confirm suspicious, invalid, or missing information. Afterwards, reports are corrected locally. The complete dataset is subjected to a thorough analysis, which is then summarised into semi-annual, descriptive reports that give an overview of the current situation. These reports are publicly available at www.multiplesclerosis.cz[11].

Legal context and ethics

ReMuS was approved by the designated ethics committees of all participating hospitals, and all patients signed an informed consent form.

The data is first collected at the individual multiple sclerosis centres, which are part of the healthcare facilities. Based on a contract between the healthcare facility and IMPULS, the data is then transferred from the MS centre to IMPULS, which acts as a data controller under the GDPR. The publication of the data from the register must be approved by SCNIL and the IMPULS Managing Board. The consent of both concerned entities is necessary for the approval of the analysis.

Table 3. Main variables in ReMuS.

Patient	Demographic characteristics, date of birth, gender, employment status, pregnancy, childbirth and breastfeeding
MS history	Date of onset, onset symptoms, disease course, EDSS and individual functional subsystems, date of EDSS evaluation
Laboratory tests (upon diagnosis and onwards)	Date of test, evoked potentials, MRI, basic cerebrospinal fluid parameters + oligoclonal bands, IgG index, JCV
Relapses	Date of relapse, steroid treatment (including dose), the severity of relapse (including hospitalisation), type of relapse
Severe and life-threatening AEs	Severity, date of onset and recovery/death, symptoms, relation to DMT
Treatment	DMTs (treatment sequences, onset date, end date, administration dates, reason for discontinuation), symptomatic treatment
COVID-19	Date and type of test, symptoms, severity (including hospitalisation, ICU stay, pneumonia, and interventions), relevant comorbidities, treatment and preventive measures, vaccination (type, date, adverse events and their severity and duration)

ReMuS, the Czech national registry of patients with multiple sclerosis; MS, multiple sclerosis; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; IgG, immunoglobulin G; JCV, John Cunningham virus; AE, adverse event; DMT, disease-modifying therapy; ICU, intensive care unit.

RESULTS

All patients in ReMuS

Based on the dataset from December 31, 2021, the total number of patients with data in the registry increased from 9,694 in 2013 to 19,174 in 2021. The number of alive monitored patients with CIS or definite MS in ReMuS rose from 9,019 in 2013 (referred from seven of 15 MS centres) to 12,940 in 2016 (referred from all 15 Czech MS centres) to 17,478 in 2021 (Fig. 1). In these years, the percentage of patients treated with DMTs in the registry ranged between 76 and 83%, but the proportion of patients treated with HE-DMTs has increased significantly (from 16.2% in 2013 to 37.1% in 2021). The rate of increase became more accentuated after 2018 (Fig. 2). Approximately 12–22% of patients (both treatment-naive and pre-treated) started a new DMT each year, and 80–85% continued this treatment the following year. In general, 9–14% of patients discontinued or switched DMT each year (Table 1).

Treatment-naive patients initiating DMTs

During the follow-up period, 8,503 treatment-naive patients initiated their first DMTs (approximately 700–1000 patients yearly). The average age at MS onset ranged from 32 to 35 years, the percentage of males from 27 to 33%, EDSS at DMT initiation was slightly above two, and the median time from MS onset to DMT initiation was around six months with a decreasing trend (Table 2, Fig. 3).

The proportion of treatment-naive patients (all MS phenotypes) starting HE-DMTs increased from 2.1% in 2013 to 18.9% in 2020 and 18.5% in 2021, with the most significant increase in 2018, when the first DMT (a HE-DMT) was approved for the treatment of primary progressive MS (PPMS) (Fig. 4). The proportion of treatment-naive patients with PPMS initiating HE-DMTs was 4.3%, 7.8%, 10.1%, and 7.0%, respectively, each year from 2018.

Patients who initially started on HE-DMTs tended to be younger, up until 2018, when this trend switched. Except for 2012 and 2017, more men initially started on HE-DMTs, especially after 2018. Throughout the whole follow-up period, treatment-naive patients starting on HE-DMTs had higher EDSS at DMT initiation (approximately 3–4) and a longer time from MS onset to DMT initiation (mean about 6–9 years) (Table 2).

As for treatment-naive patients who initially started P-DMTs, those who experienced more than one relapse before DMT initiation (P-DMT 2+R) tended to be younger, more probably women, with higher EDSS and a longer time from MS onset to DMT initiation than those who experienced only one relapse (P-DMT 1R). On the other hand, compared to patients who initially started on HE-DMTs, P-DMT 2+R had lower EDSS and, except for 2015, a shorter time from MS onset to DMT initiation. There was also a more pronounced sex difference – patients who initially started on HE-DMT were more likely men than patients who initially started on P-DMT after more than one relapse (Table 2).

DISCUSSION

The Czech National Registry, ReMuS, has proven its value since 2013. Reaching a level of 17,478 actively monitored patients out of an estimated 22,000 patients with MS in the Czech Republic in 2021, ReMuS provides a comprehensive overview of MS care in real-world clinical practice using a wide range of regularly collected and controlled variables. The rapid growth in the number of active patients included reflects the effective collaboration between the IMPULS Endowment Fund and the 15 MS centres in the Czech Republic, the presence of reliable infrastructure tools for data collection, and a diligent system of data quality control.

As the evidence of significant benefits from HE-DMTs, especially if initiated early, is growing[3–10], this study aimed

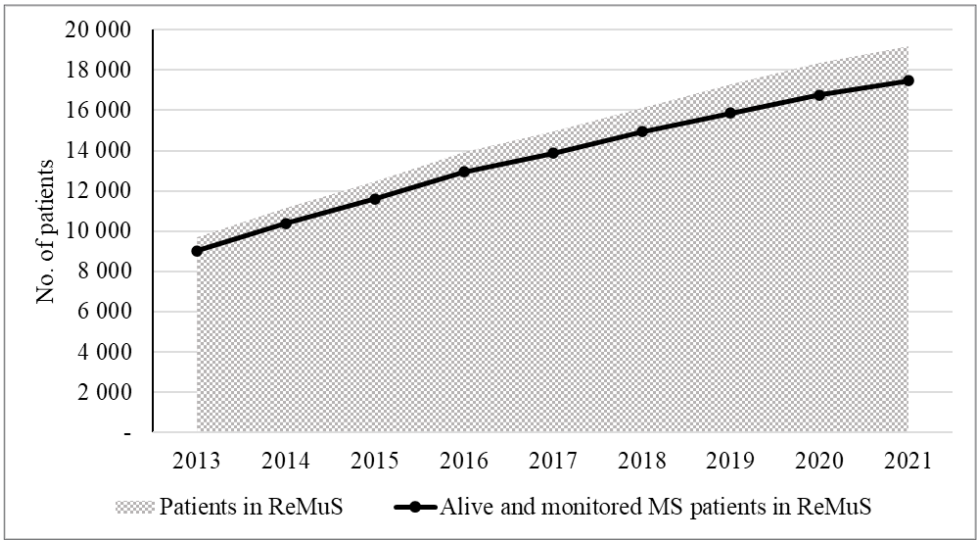

Fig. 1. Number of patients in the ReMuS registry over time.
MS, multiple sclerosis.

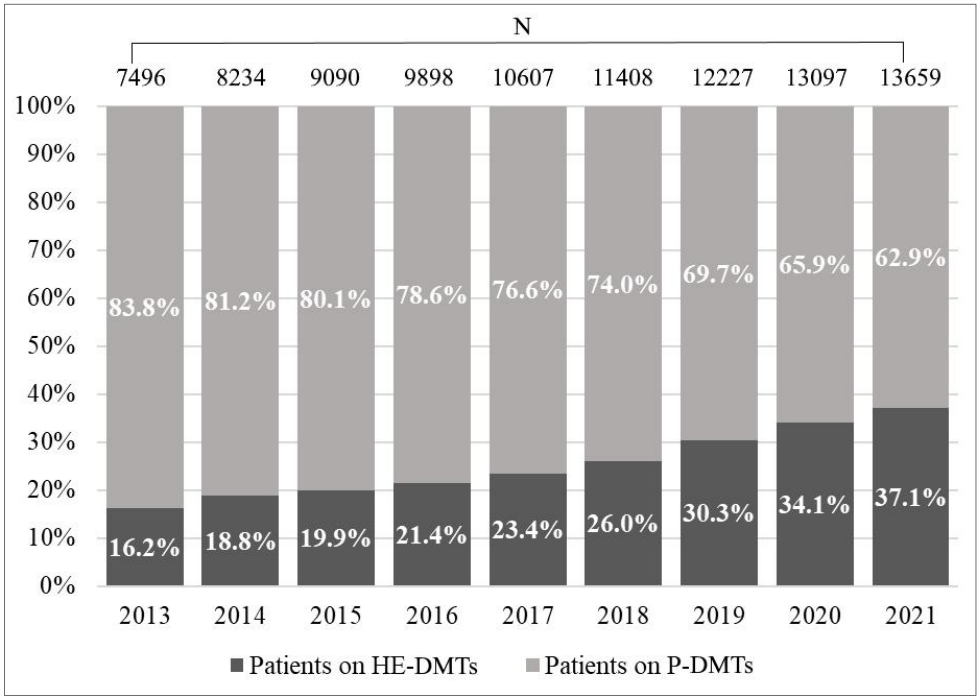

Fig. 2. The ratio of patients on HE-DMTs versus P-DMTs as of December 31st of the respective year.
P-DMT, platform disease-modifying therapy (interferons, glatiramer acetate, teriflunomide, dimethyl fumarate); HE-DMT, high-efficacy disease-modifying therapy (alemtuzumab, cladribine, S1P modulators, anti-CD20 therapies, natalizumab).

to evaluate the timeliness and representation of DMTs in real-world clinical practice, where reimbursement criteria also limit options. The good news is that despite numerous obstacles in real-world clinical practice, there is an increase in the number of patients treated with HE-DMTs. This is in accordance with the trend in many other countries[3,20,21]. The proportion of patients treated with HE-DMTs has increased from 16.2% in 2013 to 37.1% in 2021. The rate of increase became even more accentuated after 2018 when the first HE-DMT was approved for treating patients with primary-progressive MS. In addition, we expect a further increase in the proportion of patients on HE-DMTs in light of the growing knowledge of the benefits of a more aggressive approach and increasingly favourable reimbursement criteria.

In addition to the increase in the overall proportion of patients treated with HE-DMTs, there has also been an increase in the proportion of treatment-naive patients starting HE-DMTs: from 2.1% in 2013 to 18.9% in 2020 and 18.5% in 2021, with the most significant increase in 2018, when a large proportion of primary-progressive MS patients were allowed to start HE-DMTs. The change in reimbursement criteria, reflected in the ratio of MS phenotypes among DMT-treated patients, also explains other phenomena. Patients who initially started on HE-DMTs tended to be younger, but this trend switched in 2018. In the same year, there was a significant increase in the mean time from MS onset to the first DMT, as a result of the new approach to DMTs for PPMS patients. However, despite the influence of PPMS patients, the positive continuous downward trend of the median time from MS onset to the first DMT can still be seen each year since the ReMuS establishment.

Except for 2012 and 2017, more men initially started

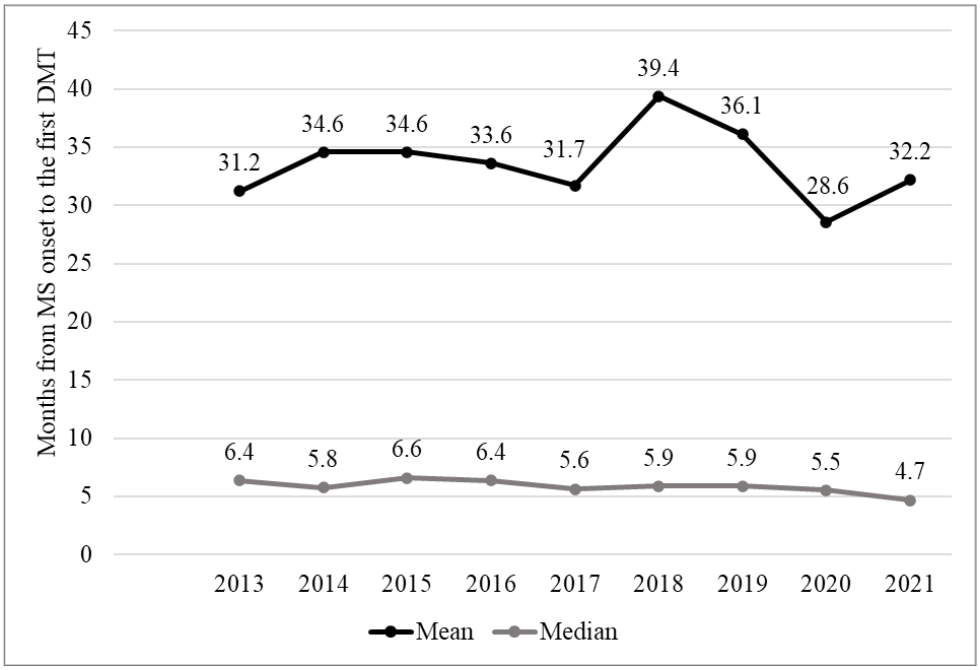

Fig. 3. Months from MS onset date to the first DMT by the year of its initiation. MS, multiple sclerosis; DMT, disease-modifying therapy.

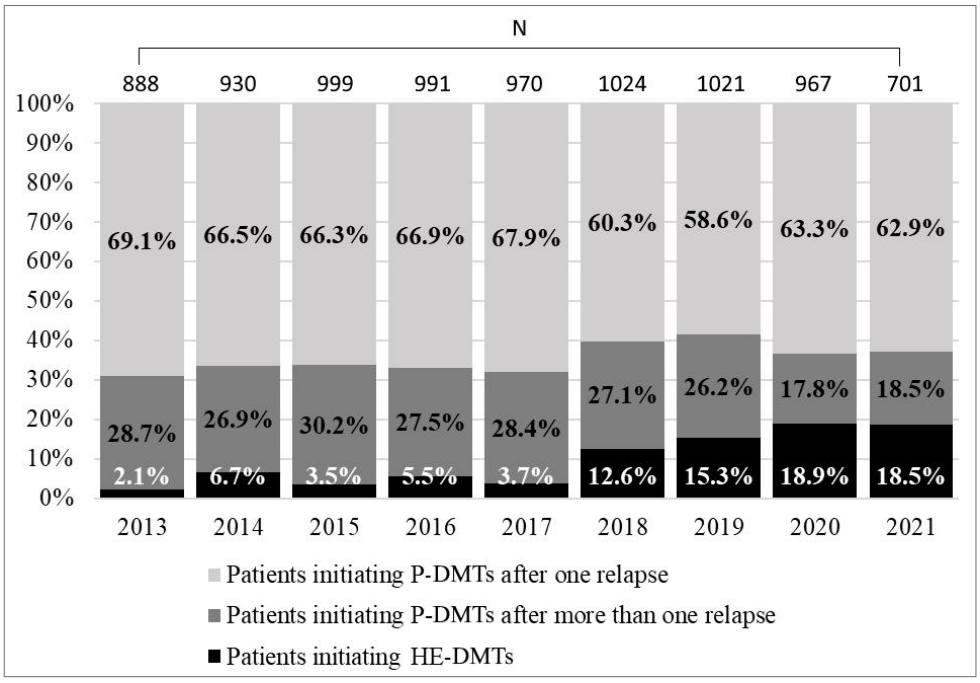

Fig. 4. The ratio of treatment-naive patients initiating their treatment with HE-DMTs and P-DMTs. P-DMT, platform disease-modifying therapy (interferons, glatiramer acetate, teriflunomide, dimethyl fumarate); HE-DMT, high-efficacy disease-modifying therapy (alemtuzumab, cladribine, S1P modulators, anti-CD20 therapies, natalizumab).

on HE-DMTs, especially after 2018. There are probably three main reasons for this. First, pregnancy planning is often considered when choosing a DMT. Second, the proportion of men is higher in primary-progressive than in relapse-remitting MS (ref.[22]), and third, the male sex is regarded as a negative prognostic factor[23].

Throughout the whole follow-up period, treatment-naive patients starting on HE-DMTs had higher EDSS at DMT onset and a longer time from MS onset to DMT initiation. This phenomenon points to the consideration of these negative prognostic features[23] by both physicians and reimbursement criteria. On the other hand, there was also a group of patients who theoretically could have met the reimbursement criteria for HE-DMTs but did not receive this treatment – those who experienced more than one relapse before DMT onset. Compared to patients who initially started on HE-DMTs, P-DMT 2+R had fewer negative prognostic markers[23] – lower EDSS and, except for 2015, a shorter time from MS onset to DMT initiation. There was also a more pronounced sex difference – patients who initially started on HE-DMT tended to be more likely men compared to P-DMT 2+R. Again, the reason may be the representation of primary-progressive patients in the HE-DMT group and also pregnancy planning.

Overall, our findings show a positive trend in the increasing proportion of patients treated with HE-DMTs, especially in the treatment-naive (even if we exclude patients with PPMS). However, we must not forget the other

side of the coin. Although early initiation of HE-DMT can provide considerable benefits, it also carries greater potential risks. Comorbidities, older age, and other factors that are usually not considered in clinical trials should also be taken into account. Consistent long-term follow-up of patients in real-world clinical practice, which only registries including ReMuS allow, is therefore crucial.

This study has several limitations. First, the aim was only to describe trends between 2013 and 2021. A more detailed analysis would have to be performed to discern the effectiveness and safety of individual therapeutic strategies. Second, since our stratification of patients partially depended on the number of relapses before starting DMTs, it may have been affected by an incomplete record of relapses. Another potential limitation was not considering the MS phenotype in the stratification. Despite this, we believe that the presented paper provides valuable insight into the development of treatment in real-world clinical practice in the Czech Republic and explains the importance of patient registries.

CONCLUSION

Patient registries, including ReMuS, provide an essential quality data source, especially in light of the increasing percentage of patients on HE-DMTs. Although early initiation of HE-DMT can provide considerable benefits, it also carries greater potential risks. Consistent long-term follow-up of patients in real-world clinical practice, which only registries allow, is therefore crucial not only to evaluate the efficacy and safety of therapeutic strategies and for epidemiological research, but also to help healthcare providers and regulatory authorities in their decision-making.

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