Untreated patients with multiple sclerosis: a study of French expert centers.

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Abstract

Background: Disease modifying therapies (DMTs), have an impact on relapses and disease progression. Nonetheless, many patients with multiple sclerosis (pwMS) remain untreated. The objective of the present study was to determine the proportion of untreated patients with multiple sclerosis (pwMS) followed in expert centers in France and determine the predictive factors of non-treatment.

Methods: Retrospective cohort study. Data were extracted from the 38 centers participating in the European Database for Multiple Sclerosis (EDMUS) on 12/15/2018 and pwMS seen at least once during the study period (from June 15, 2016 to June 14, 2017) were included.

Results: Among the 21,189 pwMS (age 47.1±13.1; EDSS 3.4±2.4), 6,631 (31.3%; 95%CI=30.7-31.9) of the patients were not receiving any DMT. Although patients with a relapsing-remitting course (n = 11,693) were the most likely to receive DMT, 14.8% (95%CI = 14.2-15.4) were still untreated (6.8% never treated). After multivariate analysis among relapsing-remitting pwMS, the main factors explaining never having been treated were not having ≥9 lesions on brain MRI (OR = 0.52 [0.44-0.61]) and lower EDSS (OR = 0.78 [0.74-0.82]). Most patients with progressive MS (50.4% for secondary and 64.2% for primary

progressive MS) did not receive any DMT during the study period, 11.6% for secondary and 34.0% for primary progressive MS had never received any DMT.

Conclusion: A significant proportion of pwMS did not receive any DMT, even though such treatments are reimbursed by the healthcare system for French patients. This result highlights the unmet need for current DMTs for a large subgroup of pwMS.

Introduction

It is now well-recognized that disease modifying therapies (DMTs), especially those that are more effective, have a major impact on relapses and even disease progression[1–3]. Thus, DMTs should be proposed as soon as possible after a diagnosis of multiple sclerosis (MS), including patients with clinically isolated syndrome (CIS) that fulfills the current diagnostic criteria for MS[4,5]. As recommended, it is also possible to offer DMT to patients with CIS and an abnormal MRI with lesions suggestive of MS who do not fulfill MS criteria[4]. Estimates of the number of patients with MS (pwMS) who remain untreated post-diagnosis are very limited, with 28% in a large cohort of Danish patients and 43% in the USA[6]. In France, DMTs are fully reimbursed by the health care system for all the patients, which is not the case in most countries in the world[7]. Nonetheless, many patients remain untreated.

Certain situations can explain why patients are untreated. Some patients have never been treated, either as no DMT was proposed or a DMT was proposed but declined. Other patients may have tried one or more DMTs and stopped for multiple reasons, in particular side effects or inefficacy. Finally, some patients may be waiting to initiate DMT. As DMTs are very expensive in many countries, costing more than $70,000 per year for most in the USA, the cost can obviously be a limiting factor for access[8]. In France, pwMS have access to DMTs at no personal expense. Thus, the cost has no impact on the treatment decision and receiving a DMT relies on the efficacy and side effects of the DMT and the preference of the patient.

We aimed to assess the proportion of untreated pwMS followed in MS expert centers in France and define predictive factors for not being treated.

Patients and Methods

Study design

This study was carried out in MS expert centers participating in the *Observatoire Français de la Sclérose en Plaques* (OFSEP) and collecting a minimal set of data prospectively at each visit for their local node of the European Database for Multiple Sclerosis (EDMUS)[9,10] (see Appendix 1 for protocol approval, registration and obtention of patient consent).

Data collection

OFSEP gathers data on patients with MS collected by all French expert MS centers and MS networks routinely using EDMUS software as a medical file for all their MS patients[9]. Patients are included when diagnosed with MS according to ongoing criteria, with no age limit. Clinical data are retrospectively collected at the first visit and prospectively thereafter during routine follow-up visits, usually at least once a year. Data collection is based on a minimal required dataset, including demographic and socioeconomic characteristics and a description of the MS and DMTs, although much more data can be collected at the investigator's discretion.

The centralized data were extracted from the EDMUS database on December 15th, 2018.

Definition of outcome measures

The primary outcome was the proportion of patients who did not receive any DMT during the one-year timeframe (from June 15, 2016 to June 14, 2017), including DMTs received during clinical trials.

The secondary outcomes consisted of those necessary to define the predictive factors for not being treated. Thus, demographic data (age, gender, follow-up center), disease data (disease course, duration of MS, EDSS, number of lesions on the latest brain MRI, relapses during the five years prior to the period of interest), and treatment data (previous DMTs with reasons for discontinuation and DMTs initiated after the study period, duration of DMT use) were recorded. Three treatment groups were defined: currently-treated patients (pwMS receiving a DMT during the study period), currently-untreated patients (pwMS not receiving any DMT during the study period but who received a DMT either before or after this period of time), and never-treated patients.

Statistical analysis

Univariate and multivariable analyses were conducted to predict the risk of being untreated taking into account center as random-effect (see Appendix 2 for further details). A two-sided p value <0.05 was considered statistically significant and no correction for familywise error was performed for exploratory analyses[11]. As proposed by Feise, particular attention was given to effect size and not only to statistical significance[12]. All analyses were performed using Stata (version 15, StataCorp, College Station, USA) software.

We additionally used R (R Core Team, 2020) with rpart to perform a decision-tree based analysis[13]. Complexity parameter (cp) was set using printcp to define the optimal number of nodes of the tree.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

During the study period (June 15, 2016 to June 14, 2017), 22,252 patients were seen at least once in one of the participating French MS centers and 21,189 were eligible for the present study (**Figure 1**). Among them, 14,558 (68.7%, 95%CI=68.1-69.3) were receiving a DMT (currently treated patients), 3,122 (14.7%, 95%CI=14.3-15.2) had never used a DMT (untreated patients), and 3,509 (16.6%, 95%CI=16.1-17.1) had received treatment outside the study period (currently untreated, 174 (0.8%) received a DMT in the 6 months after the period of interest, whereas others had been treated before study period). Thus, 31.3% (95%CI=30.7-31.9) of the patients were not receiving any DMT during the one-year timeframe of the study, including 14.8% (95%CI=14.2-15.4) of patients with RR-MS.

Among the centers with at least 50 patients seen during the study period (33/38), the proportion of never-treated patients varied from 10.4 to 25.4%. Similarly, the proportion of untreated patients varied from 17.8 to 42.6%. A decision tree-based analysis was performed and showed that the most important parameter explaining never having been treated was the disease course (see **Figure S1**). Indeed, patients with RR- or SP-MS were more likely to have tried at least one treatment.

Demographic and clinical characteristics of the overall population and the three sub-groups according to DMT status are presented in **Table 1**. As there is an obvious difference in DMT use according to the disease course, the characteristics of the included patients are presented in specific tables for each disease course.

Relapsing remitting MS

Never treated RR-MS patients had a milder disease course, as shown by a longer duration of disease, a lower EDSS, a lower ARR, and a smaller number of lesions on brain MRI than currently treated RR-MS patients (**Table 2**). Currently treated RR-MS patients had been treated for 60.8% of the time since MS onset (first DMT initiated 4.6±5.9 years after disease onset, 0.29±0.64 relapse during the year before initiation of the current DMT) and previously treated patients had been treated for 36.3% of the time. Previously treated RR-MS patients had received a median number of two DMTs (IQR [1 – 3]). They mainly stopped their DMTs due to side effects (39%), a scheduled stop (18%), inefficacy (16%), personal convenience (15%), or pregnancy (7%). DMTs most frequently used for current and past users are presented in **Table S1**.

After multivariate analysis, the probability of never having been treated was explained by not having ≥9 lesions on brain MRI (OR=0.52 [0.44-0.61]), lower EDSS (OR=0.78 [0.74-0.82]), and higher age (OR=1.04 [1.03-1.05]). The probability of having stopped a previous DMT and being currently untreated was explained by not having ≥9 lesions on brain MRI (OR=0.70 [0.60-0.82]), being female (OR=1.34 [1.11-1.61]), lower ARR (OR=0.88 [0.80-0.97]), higher EDSS (OR=1.07 [1.03-1.12]), longer disease duration (OR=1.02 [1.01-1.03]), and higher age (OR=1.03 [1.02-1.03]).

Single relapse

Patients with a single relapse were younger than RR-MS patients (**Table 3**). Never-treated patients had less frequently ≥9 lesions on brain MRI and a median disease duration of only 1.1 years, whereas previously treated patients had been followed for much longer (median of 7.2 years) and still had a low EDSS. Currently-treated patients and those initiating a DMT in the following six months were more prone to have fulfilled all of the 2010 McDonald criteria at the last follow-up visit than untreated patients. Previously treated patients with a single

relapse received a median number of one DMT (IQR [1 – 2]), which was stopped mainly due to side effects (39%), personal convenience (23%), a scheduled stop (21%), pregnancy (10%), or inefficacy (4%). Currently-treated patients had used a DMT for 70.5% of the time since the single relapse (first DMT initiated 1.4±2.7 years after the event), whereas previously treated patients had used a DMT for 43.4% of the time. DMTs most frequently used for current and past users are presented in **Table S1**.

After multivariate analysis, the probability of never having been treated was explained by not fulfilling the 2010 McDonald criteria at last follow-up (OR=0.37 [0.31-0.45]), not having ≥9 lesions on brain MRI (OR=0.41 [0.34-0.50]), shorter disease duration (OR=0.90 [0.88-0.93]), and higher age (OR=1.02 [1.01-1.03]). The probability of having stopped a previous DMT and being currently untreated was explained by longer disease duration only (OR=1.11 [1.07-1.14]).

Secondary progressive MS

Untreated SP-MS patients were older, with a longer duration of disease, in particular those who had never been treated (**Table 4**). They had a lower ARR during the preceding five years. Previously treated SP-MS patients had the highest EDSS and the lowest relapse rate. They had received a median of three DMTs (IQR [2 – 4]). They mainly stopped their DMTs due to inefficacy (32%), a scheduled stop (26%), side effects (22%), personal convenience (8%), or pregnancy (0.4%). Currently-treated SP-MS patients had spent 53.5% of the time using a DMT since disease onset (first DMT initiated 9.0±8.5 years after disease onset, 0.08 ± 0.30 relapse during the year prior current DMT initiation), whereas previously treated patients had received a DMT for 32.0% of the time. DMTs most frequently used for current and past users are presented in **Table S1**.

After multivariate analysis, as for the RR-MS patients, the probability of never having been treated was explained by: lower ARR (OR=0.64 [0.50-0.82]), lower EDSS (OR=0.71 [0.66-0.77]), and higher age (OR=1.06 [1.05-1.08]). The probability of having stopped a previous DMT and being currently untreated was explained by lower ARR (OR=0.70 [0.61-0.81]), higher EDSS (OR=1.44 [1.36-1.52]), longer disease duration (OR=1.02 [1.01-1.02]), and higher age (OR=1.02 [1.01-1.03]).

Primary progressive MS

Never treated PP-MS patients were significantly older and had a statistically lower EDSS, although the difference was not clinically meaningful (**Table 5**). They had had fewer relapses during the five previous years. Previously-treated patients were older, with a higher EDSS and a lower relapse rate than those being currently treated. They had received a median of two DMTs (IQR [1 – 3]). They mainly stopped their DMT due to inefficacy (33%), a scheduled stop (30%), side effects (21%), personal convenience (7%), or pregnancy (0.1%). Currently-treated PP-MS patients had spent 44.7% of the time using a DMT since disease onset (initiated 5.8±5.7 years after disease onset, 0.09±0.31 relapse during the year prior to current DMT initiation), whereas previously treated patients had received a DMT for 26.8% of the time. DMTs most frequently used for current and past users are presented in **Table S1**.

After multivariate analysis, the probability of never having been treated was explained by a lower EDSS (OR=0.74 [0.69-0.79]), higher age (OR=1.05 [1.04-1.06]), and shorter disease duration (OR=0.97 [0.96-0.99]). The probability of having stopped previous DMT and being currently untreated was explained by a higher EDSS (OR=1.51 [1.40-1.63]), lower ARR (OR=0.73 [0.55-0.98]), and longer disease duration (OR=1.04 [1.03-1.05]).

Discussion

In this nation-wide, tertiary care-center study, 31% of pwMS were not receiving a DMT during the one-year study period (June 2016 to June 2017) and 15% had never received any DMT. Even taking only patients with RR-MS into account, 7% had never received any DMT and 15% were not being treated during the study period. Moreover, even currently-treated patients were quite far from having been treated all the time since disease onset (61% of the time for currently-treated RR-MS patients). Nearly 40% of patients with a single relapse and RR-MS patients that were previously treated stopped their DMT due to side effects. The patients that were less likely to receive DMT were patients with progressive-MS.

Many DMTs are currently available for relapsing MS. In addition, it is now well-demonstrated that early effective treatment reduces long-term disability[3,14–16]. Despite these data and although access to treatment is easy for all French patients and reimbursed by the healthcare system, the number of untreated pwMS among those seen in expert centers is high. The proportion of untreated patients is close to that reported in a large Danish cohort, in which 28% of patients were untreated. This European country has a similar social system to that of France, with a minimal cost of treatment for the patients[6]. In the same study, it was noted that 43% of US pwMS were untreated. A previous nation-wide study was conducted in France, including all pwMS in the French national health insurance databases (97% of the French general population). Patients were identified over the period from 2010 to 2015[17]. In this exhaustive study, 46% of the French MS population was untreated. Compared to the 31% observed for patients seen in MS expert centers, it is probable that patients followed in such centers are more prone to take a DMT and/or that neurologists working in these centers are more prone to propose a DMT, although there is a center effect. Of note, 26% of the pwMS had never consulted a neurologist during the six year-period of the previous study[17]. The untreated group is composed of a large majority of progressive MS patients (68.8%). Progressive MS patients are known to present with a higher EDSS and are less frequently treated as few patients can have a benefit using currently available DMTs. Thus, the currently untreated group has the highest EDSS.

Approaches to MS management differ across Europe, based on the perceived risks and benefits of DMTs. We hypothesize that if the benefit/risk ratio was favorable for every single patient with MS, reducing the relapse risk, the risk of progression and the risk of long-term disability, without any side effect, every single patient with MS should receive a DMT. As it

is not the case, we suggest that our data support the fact that there still is an unmet need for MS treatment, especially for progressive MS. Other studies would be necessary to determine if in the long-term all patients would gain more than they could lose from DMT. However, the methodology of the present study was not suitable to know which was the reasoning behind a decision not to treat. In France, such decision is usually shared between the neurologist and the patient. Thus, if both the neurologist and the patient have the feeling that the disease is not very active, a DMT is less likely to be prescribed, especially if previously tried DMTs had induced side effects. The present data are in favour of an overall good evaluation of the benefit/risk ratio of the DMTs, patients with less to gain being reasonably identified. The most counter-intuitive result concerned the 15% of patients with RR-MS seen in an expert center that were not receiving a DMT. Even if we consider that benign MS can go untreated, these patients do not represent more than 3% of the general MS population[18], although the natural history of MS appears milder in the recent years, probably as a result of an interplay between several factors including changes in the diagnostic criteria, changes in the epidemiology of MS, impact of early and appropriate DMT and improvement of the general state of health in the population[19]. A possible explanation of why so many patients were going untreated is the prevalence of side effects, which have a strong impact on the persistence of treatment. In the present study, nearly 40% of patients with a single relapse and RR-MS patients that were previously treated stopped their DMT due to side effects and stayed untreated thereafter. Although many DMTs are available, with minimal side effects for many patients, reducing the side effects of first-line DMT is still a major challenge for improving the persistence of treatment[20,21]. This partially explains why 8% of RR-MS patients had previously been treated, with a median of two different DMTs, and were no longer being treated.

Currently-treated RR-MS patients had used a DMT for 61% of the time since disease onset. This parameter mainly highlights that many patients were not treated quickly after the first clinical event (4.6±5.9 years), as well as that there were gaps between different DMTs for some patients. Some of these gaps can be explained by pregnancy and this factor should be explored in future studies. For cases that had begun several years before, neurologists were waiting for a second event to make the diagnosis and propose a DMT. As the diagnosis can be made faster with more recent criteria[22,23], it will be informative in the future to explore whether the time between the first clinical event and DMT initiation decreases and the proportion of time receiving a DMT increases. Therapeutic inertia is prone to slow down

such changes in management, although such phenomenon is supposed to be less pronounced in tertiary care centers with neurologists with a high expertise for MS care [24].

Until recently, few therapeutic options, other than symptomatic treatment, were available for patients with progressive MS[25,26]. Ocrelizumab was approved in 2017 for patients with early-stage PP-MS[27] and siponimod in 2019 for SP-MS, associated with clinical or radiological inflammatory activity[28]. Although DMTs used during clinical trials were included, the lack of labeled effective treatments during the study period explains the low prevalence of DMT use in this sub-group, particularly for PP-MS. In addition, in other observational studies, patients >60 years of age and those with SP-MS had no major risk when discontinuing DMT[29,30]. Despite these obvious limits, around 45% of all progressive MS patients were receiving a DMT. In this sub-group, anti-CD20, were used in a significant proportion of patients during study period, probably anticipating ocrelizumab's approval. For patients with non-active progressive MS, mycophenolate mofetil and methotrexate were frequently used (Table S1), although these drugs are not approved and have very limited evidence of efficacy [31,32]. We hypothesize that it is difficult to accept for some patients not to receive any DMT, especially when they are seeking care in a tertiary center, and that neurologists propose in such cases treatments with low perceived risk.

As the present study was conducted on data acquired from 2016 to 2017, it is understandable that patients with a single relapse who did not fulfil the 2010 McDonald criteria (31%) were infrequently receiving a DMT. Fulfilling or not the McDonald criteria at the end of the follow up was the most important variable explaining the use or not of a DMT (70% fulfilling the criteria for those receiving a DMT and 45% for those who were not). Since the publication of the new MS diagnostic criteria[33], more patients experiencing typical CIS can be diagnosed with MS and receive a DMT. Thus, performing the same study in the near future, focusing on data acquired since 2018, may show a change in practice, with more patients with CIS receiving a DMT.

Limitations

First, this study was conducted in MS expert centers. Thus, it corresponds to tertiary care and cannot be extrapolated to all MS patients (21,189 patients seen among the 100,000 pwMS in France). As discussed above, the proportion of treated patients is lower in the general MS population. Indeed, some of these patients do not even see a neurologist. Thus, the true number of untreated pwMS is even higher than that reported in the present study. Second, we

don't have information concerning who decided not to treat. Most neurologists share the decision with the patients, but in some cases, we can imagine that the decision was mainly coming from the patients and in others, from the neurologists. Third, it is not possible to know whether patients with a single clinical event fulfilled the 2017 McDonald criteria for RR-MS. Only data concerning the 2010 criteria were available, although such a parameter could have had an influence on the treatment decision. Fourth, among never-treated MS patients, some may have been seen in an MS expert center for the first time during the study period and the diagnosis made retrospectively at that point. Thus, it is understandable that these patients were not treated before the diagnosis was made. Fifth, spinal cord lesion load can have an impact on treatment decision. Unfortunately, only a minority of patients (8134/21189, i.e. 38.4%) had at least one spinal MRI recorded in the database and we decided not to use such data. Finally, to know whether the absence of DMT use is deleterious would require a follow-up of at least two years to assess the evolution of the EDSS, which was not possible with the design of the present study.

In conclusion, the present study shows that a significant proportion of pwMS followed in expert centers were not receiving DMT, including 15% of patients with RR-MS, despite a large choice of effective and generally well-tolerated treatments. Patients with a single clinical event and progressive MS were less likely to receive a DMT. These results are likely to evolve in the coming years, with a higher proportion of patients treated, as diagnostic criteria have evolved for first demyelinating events and as new treatments are now available for progressive MS. Nonetheless, these results highlight several of the unmet medical needs in the treatment of pwMS.

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Conflicts of interest:

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References

1. Brown JWL, Coles A, Horakova D, et al. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. *JAMA*. 2019;321(2):175-187. doi:10.1001/jama.2018.20588

2. Harding K, Williams O, Willis M, et al. Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis. *JAMA Neurol*. 2019;76(5):536-541. doi:10.1001/jamaneurol.2018.4905

3. Ontaneda D, Tallantyre E, Kalincik T, Planchon SM, Evangelou N. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. *Lancet Neurol*. 2019;18(10):973-980. doi:10.1016/S1474-4422(19)30151-6

4. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl*. 2018;24(2):96-120. doi:10.1177/1352458517751049

5. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(17):789-800. doi:10.1212/WNL.0000000000005345

6. Nørgaard M, Foch C, Magyari M, et al. Untreated Patients with Multiple Sclerosis: Prevalence and Characteristics in Denmark and in the United States (P4.2-060). *Neurology*. 2019;92(15 Supplement):P4.2-060.

7. Simacek KF, Ko JJ, Moreton D, Varga S, Johnson K, Katic BJ. The Impact of Disease-Modifying Therapy Access Barriers on People With Multiple Sclerosis: Mixed-Methods Study. *J Med Internet Res*. 2018;20(10). doi:10.2196/11168

8. Hartung DM. Economics and Cost-Effectiveness of Multiple Sclerosis Therapies in the USA. *Neurother J Am Soc Exp Neurother*. 2017;14(4):1018-1026. doi:10.1007/s13311-017-0566-3

9. Vukusic S, Casey R, Rollot F, et al. Observatoire Français de la Sclérose en Plaques (OFSEP): A unique multimodal nationwide MS registry in France. *Mult Scler Houndmills Basingstoke Engl*. 2020;26(1):118-122. doi:10.1177/1352458518815602

10. Confavreux C, Compston DA, Hommes OR, McDonald WI, Thompson AJ. EDMUS, a European database for multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1992;55(8):671-676.

11. Bender R, Lange S. Adjusting for multiple testing--when and how? *J Clin Epidemiol*. 2001;54(4):343-349. doi:10.1016/s0895-4356(00)00314-0

12. Feise RJ. Do multiple outcome measures require p-value adjustment? *BMC Med Res Methodol*. 2002;2:8.

13. Krzywinski M, Altman N. Classification and regression trees. *Nat Methods*. 2017;14(8):757-758. doi:10.1038/nmeth.4370

14. Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet Lond Engl*. 2007;370(9585):389-397. doi:10.1016/S0140-6736(07)61194-5

15. Leray E, Yaouanq J, Le Page E, et al. Evidence for a two-stage disability progression in multiple sclerosis. *Brain J Neurol*. 2010;133(Pt 7):1900-1913. doi:10.1093/brain/awq076

16. Chalmer TA, Baggesen LM, Nørgaard M, et al. Early versus later treatment start in multiple sclerosis: a register-based cohort study. *Eur J Neurol*. 2018;25(10):1262-e110. doi:10.1111/ene.13692

17. Roux J, Guilleux A, Grimaud O, Leray E. Care-seeking of patients with multiple sclerosis over 2010-2015 in France: a nationwide study using health administrative data. ECTRIMS Online Library. P1000. Published 2018. Accessed May 14, 2020. https://onlinelibrary.ectrims-congress.eu/ectrims/2018/ectrims-2018/228842/jonathan.roux.care-seeking.of.patients.with.multiple.sclerosis.over.2010-2015.html

18. Tallantyre EC, Major PC, Atherton MJ, et al. How common is truly benign MS in a UK population? *J Neurol Neurosurg Psychiatry*. 2019;90(5):522-528. doi:10.1136/jnnp-2018-318802

19. Sorensen PS, Sellebjerg F, Hartung H-P, Montalban X, Comi G, Tintoré M. The apparently milder course of multiple sclerosis: changes in the diagnostic criteria, therapy and natural history. *Brain J Neurol*. 2020;143(9):2637-2652. doi:10.1093/brain/awaa145

20. Condé S, Moisset X, Pereira B, et al. Dimethyl fumarate and teriflunomide for multiple sclerosis in a real-life setting: a French retrospective cohort study. *Eur J Neurol*. Published online October 15, 2018. doi:10.1111/ene.13839

21. Lahdenperä S, Soilu-Hänninen M, Kuusisto H-M, Atula S, Junnila J, Berglund A. Medication adherence/persistence among patients with active multiple sclerosis in Finland. *Acta Neurol Scand*. Published online June 19, 2020. doi:10.1111/ane.13301

22. Brownlee WJ, Swanton JK, Altmann DR, Ciccarelli O, Miller DH. Earlier and more frequent diagnosis of multiple sclerosis using the McDonald criteria. *J Neurol Neurosurg Psychiatry*. 2015;86(5):584-585. doi:10.1136/jnnp-2014-308675

23. McNicholas N, Lockhart A, Yap SM, et al. New versus old: Implications of evolving diagnostic criteria for relapsing-remitting multiple sclerosis. *Mult Scler Houndmills Basingstoke Engl*. 2019;25(6):867-870. doi:10.1177/1352458518770088

24. Almusalam N, Oh J, Terzaghi M, et al. Comparison of Physician Therapeutic Inertia for Management of Patients With Multiple Sclerosis in Canada, Argentina, Chile, and Spain. *JAMA Netw Open*. 2019;2(7):e197093. doi:10.1001/jamanetworkopen.2019.7093

25. Fox RJ, Thompson A, Baker D, et al. Setting a research agenda for progressive multiple sclerosis: the International Collaborative on Progressive MS. *Mult Scler Houndmills Basingstoke Engl*. 2012;18(11):1534-1540. doi:10.1177/1352458512458169

26. Shirani A, Okuda DT, Stüve O. Therapeutic Advances and Future Prospects in Progressive Forms of Multiple Sclerosis. *Neurother J Am Soc Exp Neurother*. 2016;13(1):58-69. doi:10.1007/s13311-015-0409-z

27. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med*. 2017;376(3):209-220. doi:10.1056/NEJMoa1606468

28. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet Lond Engl*. 2018;391(10127):1263-1273. doi:10.1016/S0140-6736(18)30475-6

29. Bonenfant J, Bajeux E, Deburghgraeve V, Le Page E, Edan G, Kerbrat A. Can we stop immunomodulatory treatments in secondary progressive multiple sclerosis? *Eur J Neurol*. 2017;24(2):237-244. doi:10.1111/ene.13181

30. Hua LH, Fan TH, Conway D, Thompson N, Kinzy TG. Discontinuation of disease-modifying therapy in patients with multiple sclerosis over age 60. *Mult Scler Houndmills Basingstoke Engl*. 2019;25(5):699-708. doi:10.1177/1352458518765656

31. Michel L, Vukusic S, De Seze J, et al. Mycophenolate mofetil in multiple sclerosis: a multicentre retrospective study on 344 patients. *J Neurol Neurosurg Psychiatry*. 2014;85(3):279-283. doi:10.1136/jnnp-2013-305298

32. Goodkin DE, Rudick RA, VanderBrug Medendorp S, et al. Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. *Ann Neurol*. 1995;37(1):30-40. doi:10.1002/ana.410370108

33. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173. doi:10.1016/S1474-4422(17)30470-2

Table 1. Description of the overall population and the three sub-groups according to disease modifying treatment use. Never treated (A), Currently untreated (B), Currently treated (C). Statistical comparisons performed using the Tukey-Kramer or Dunn tests. A two-sided p value < 0.05 was considered statistically significant. RR: relapsing remitting with at least 2 relapses, SP: secondary progressive, PP: primary progressive.

Table 2. Presentation of the four sub-groups of patients with relapsing-remitting multiple sclerosis (RR-MS). * corresponds to $p < 0.001$ for comparison with currently treated RR-MS patients. ARR: annualized relapse rate.

Table 3. Presentation of the four sub-groups of patients with a single relapse. * corresponds to $p < 0.001$ for comparison with currently-treated patients. Disease duration is expressed as the median and interquartile range, as the distribution was non-normal.

Table 4. Presentation of the four sub-groups of patients with secondary progressive multiple sclerosis (SP-MS). * corresponds to $p < 0.001$ for comparison with currently-treated SP-MS patients.

Table 5. Presentation of the four sub-groups of patients with primary progressive multiple sclerosis (PP-MS). * corresponds to $p < 0.001$ for comparison with currently-treated PP-MS patients.

Figure 1. Flow diagram of patients seen at least once during the one-year study period (June 15, 2016 to June 14, 2017).

Supplementary files:

Table S1. Five most frequently used disease modifying therapies (DMTs) for each disease course, both previously and currently used.

Figure S1. Classification tree presenting the probability of never having been treated. RR: relapsing remitting with at least 2 relapses, SP: secondary progressive, PP: primary progressive.

Table 1. Description of the overall population and the three sub-groups according to disease modifying treatment use. Never treated (A), Currently untreated (B), Currently treated (C). Statistical comparisons performed using the Tukey-Kramer or Dunn tests. A two-sided p value < 0.05 was considered statistically significant. RR: relapsing remitting with at least 2 relapses, SP: secondary progressive, PP: primary progressive.

	Overall population N = 21,189	**Never treated N = 3,122**	**Currently untreated N = 3,509**	**Currently treated N = 14,558**	**Statistics**
Demographic characteristics					
Female sex, % (n)	71.2 (15,075)	68.9 (2,152)	69.4 (2,436)	72.0 (10,487)	
Age at disease diagnosis (years)	33.0 ± 10.8	38.2 ± 12.2	34.2 ± 10.7	31.6 ± 10.1	A≠B≠C
Age at first appointment during study period	47.1 ± 13.1	50.8 ± 14.9	54.9 ± 12.1	44.4 ± 11.9	A≠B≠C
Clinical characteristics					
Disease duration (years)	14.1 ± 10.4	12.6 ± 12.4	20.7 ± 11.0	12.9 ± 9.1	A≠B ; B≠C
Disease course, n (%)					
- Single relapse	2,718 (12.8)	985 (31.6)	158 (4.5)	1,575 (10.8)	
- RR	11,693 (55.2)	793 (25.4)	936 (26.7)	9,964 (68.4)	A≠B≠C
- SP	4,289 (20.2)	498 (16.0)	1,662 (47.4)	2,129 (14.6)	
- PP	2,489 (11.8)	846 (27.1)	753 (21.5)	890 (6.1)	
EDSS	3.4 ± 2.4	3.2 ± 2.5	5.2 ± 2.4	2.9 ± 2.2	A≠B≠C

Table 2. Presentation of the four sub-groups of patients with relapsing-remitting multiple sclerosis (RR-MS). * corresponds to $p < 0.001$ for comparison with currently treated RR-MS patients. ARR: annualized relapse rate.

	Overall RR-MS patients N = 11,693	**Currently treated N = 9,964 (85.2%)**	**Currently untreated N = 936 (8.0%)**		**Never treated N = 793 (6.8%)**
			Previously treated N = 860 (7.4%)	Treated in the 6 months after study period N = 76 (0.6%)	
Age, years	43.2 ± 11.4	42.5 ± 11.0	48.3 ± 12.4*	40.3 ± 11.7	47.3 ± 13.2*
Female sex, % (n)	75.7 (8,856)	75.1 (7,478)	80.8 (695)*	77.6 (59)	78.7 (624)
EDSS	2.3 ± 1.8	2.3 ± 1.7	2.7 ± 2.0*	2.2 ± 1.3	1.9 ± 1.7*
Disease duration, years	12.8 ± 8.5	12.4 ± 8.1	16.5 ± 9.2*	9.9 ± 8.6*	14.7 ± 11.2*
Age at disease onset, years	30.4 ± 9.5	30.1 ± 9.4	31.8 ± 10.1*	30.4 ± 9.6	32.4 ± 10.4*
MRI ≥ 9 lesions (n = 9,513)	76.9 (7,314)	78.4 (6,445)	74.3 (459)	68.1 (49)	59.5 (361)*
2-year ARR	0.32 ± 0.49	0.34 ± 0.50	0.22 ± 0.43*	0.32 ± 0.41	0.23 ± 0.36*
5-year ARR	0.33 ± 0.33	0.34 ± 0.34	0.26 ± 0.34*	0.28 ± 0.30	0.19 ± 0.22*

Table 3. Presentation of the four sub-groups of patients with a single relapse. * corresponds to $p < 0.001$ for comparison with currently-treated patients. Disease duration is expressed as the median and interquartile range, as the distribution was non-normal.

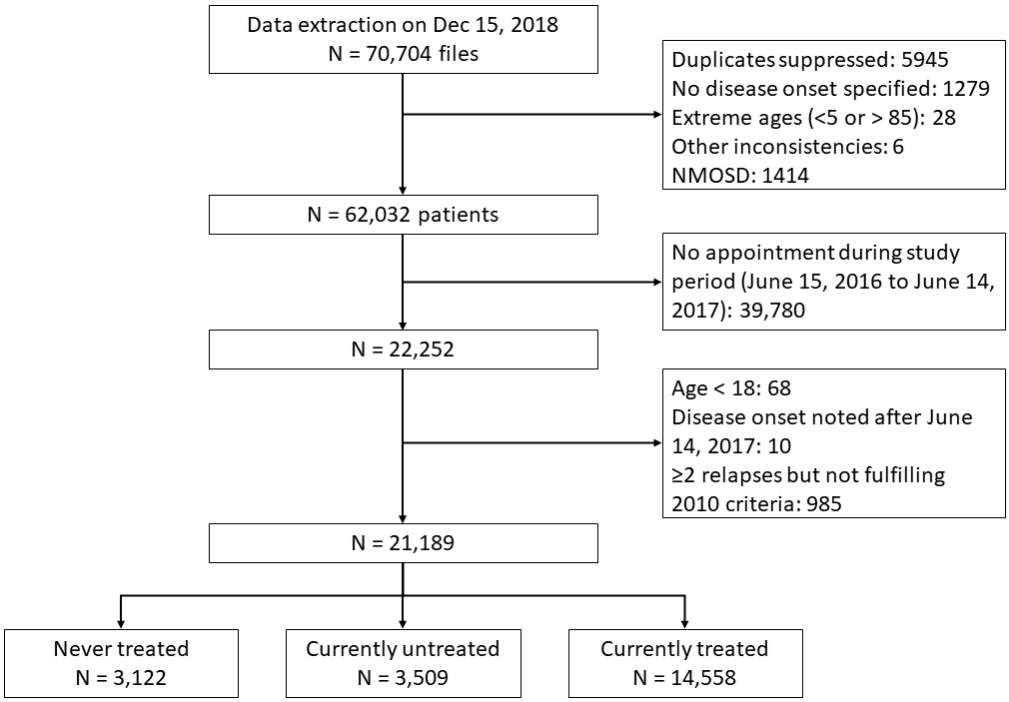
	Overall patients with a single relapse N = 2,718	**Currently treated N = 1,575 (57.9%)**	**Currently untreated N = 158 (5.8%)**		**Never treated N = 985 (36.2%)**
			Previously treated N = 107 (3.9%)	Treated in the 6 months after study period N = 51 (1.9%)	
Age, years	40.0 ± 11.9	39.2 ± 11.4	45.4 ± 11.9*	37.1 ± 10.0	40.7 ± 12.5*
Female sex, % (n)	71.0 (1,929)	70.0 (1,102)	72.9 (78)	78.4 (40)	72.0 (709)
EDSS	1.4 ± 1.5	1.4 ± 1.5	1.4 ± 1.7	1.8 ± 1.6	1.3 ± 1.5
MRI ≥ 9 lesions (n = 2,347)	58.8 (1,381)	69.7 (946)	63.5 (45)	76.5 (39)	40.4 (349)*
McDonald's 2010 criteria at last follow-up	60.6 (1,646)	70.2 (1,105)	55.1 (59)*	80.4 (41)	44.8 (441)*
Disease duration, years	2.3 [0.7-5.5]	2.9 [1.2-5.9]	7.2 [4.3-12.2]*	0.3 [0.1-2.1]*	1.1 [0.3-3.5]*
Age at disease onset, years	35.9 ± 10.8	34.9 ± 10.4	36.2 ± 9.8	35.4 ± 9.8	37.4 ± 11.3*
Optic neuritis	28.4 (772)	29.2 (460)	24.3 (26)	29.4 (15)	27.5 (271)

Table 4. Presentation of the four sub-groups of patients with secondary progressive multiple sclerosis (SP-MS). * corresponds to $p < 0.001$ for comparison with currently-treated SP-MS patients.

	Overall SP-MS patients N = 4,289	**Currently treated N = 2,129 (49.6%)**	**Currently untreated N = 1,662 (38.8%)**		**Never treated N = 498 (11.6%)**
			Previously treated N = 1,645 (38.4%)	Treated in the 6 months after study period N = 17 (0.4%)	
Age, years	56.3 ± 10.5	53.4 ± 10.1	58.3 ± 9.8*	54.6 ± 9.1	62.1 ± 10.2*
Female sex, % (n)*	68.5 (2,938)	68.2 (1,451)	69.0 (1,135)	64.7 (11)	68.5 (361)
EDSS	6.1 ± 1.4	5.8 ± 1.3	6.5 ± 1.4*	6.0 ± 1.3	5.7 ± 1.6
Disease duration, years	24.2 ± 10.2	21.7 ± 9.3	26.3 ± 10.0*	20.9 ± 10.5	27.8 ± 11.7*
Age at disease onset, years	32.2 ± 9.7	31.8 ± 9.4	32.0 ± 9.7	33.6 ± 10.5	34.3 ± 10.8*
Progressive phase duration	10.9 ± 7.6	8.7 ± 6.6	13.3 ± 7.6*	6.7 ± 5.7	12.1 ± 8.9
2-year ARR	0.14 ± 0.31	0.20 ± 0.37	0.08 ± 0.24*	0.18 ± 0.30	0.08 ± 0.21*
5-year ARR	0.17 ± 0.26	0.23 ± 0.29	0.11 ± 0.22*	0.14 ± 0.17	0.09 ± 0.15*

Table 5. Presentation of the four sub-groups of patients with primary progressive multiple sclerosis (PP-MS). * corresponds to $p < 0.001$ for comparison with currently-treated PP-MS patients.

	Overall PP-MS patients N = 2,489	**Currently treated N = 890 (35.8%)**	**Currently untreated N = 753 (30.2%)**		**Never treated N = 846 (34.0%)**
			Previously treated N = 723 (29.0%)	Treated in the 6 months after study period N = 30 (1.2%)	
Age, years	57.2 ± 11.3	53.6 ± 11.2	59.6 ± 10.2*	49.3 ± 8.4	59.3 ± 11.4*
Female sex, % (n)*	54.3 (1,352)	51.4 (456)	56.2 (406)	40.0 (12)	56.5 (478)
EDSS	5.7 ± 1.6	5.5 ± 1.5	6.5 ± 1.4*	4.8 ± 1.9	5.2 ± 1.7*
Disease duration, years	13.8 ± 9.0	12.0 ± 8.0	17.5 ± 8.5*	8.6 ± 6.8	12.6 ± 9.4
Age at disease onset, years	43.5 ± 11.1	41.6 ± 11.2	42.0 ± 10.2	40.8 ± 9.9	46.7 ± 11.0*
2-year ARR	0.07 ± 0.20	0.10 ± 0.24	0.04 ± 0.17*	0.17 ± 0.24	0.07 ± 0.18*
5-year ARR	0.09 ± 0.17	0.13 ± 0.21	0.06 ± 0.16*	0.14 ± 0.12	0.08 ± 0.12*



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