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Trends in disease-modifying therapy use in patients with multiple sclerosis using a 10-year population-based cohort study in France

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Data availability statement

According to data protection and the French regulation, the authors cannot publicly release the data from the French national health data system (SNDS). However, a request for data reuse may be made and would require the obtention of prior approval of the French regulatory authorities (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donneesandhttps://www.indsante.fr/).

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Abstract

Background*:* The availability of new disease-modifying therapies (DMTs) for patients with multiple sclerosis (MS) provides an opportunity for improving outcomes but makes disease management more complex. Our study aimed to describe changes in therapeutic practices over the period 2009-2018 and measure the impact of the arrival of oral DMTs on the use of injectable DMTs.

Methods: Data were extracted from a representative 1/97 sample of the French population covered by the healthcare insurance system. Study period was set from 1 January 2009 to 31 December 2018. Four periods of MS identification were defined (before 2009, 2009-2011, 2012-2015 and 2016-2018).

Results: Overall, 1,508 patients with MS were included, of whom 876 (58.1%) were treated at least once over the study period. Untreated patients were older and had more comorbidities than treated ones. First-line DMTs were the most frequent initial DMT (78.5%) and a shift has operated from injectable to oral drugs over time. The proportion of patients receiving several DMTs increased with the number of available drugs. End 2018, beta interferon, glatiramer acetate, teriflunomide, dimethylfumarate, fingolimod and natalizumab shared nearly equal parts.

Conclusions: This study provides valuable insights into the real-world use of DMTs and changes that have operated over time.

Keywords:

disease-modifying therapies, health administrative database, multiple sclerosis, time-series, untreated

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1. Introduction

Multiple sclerosis (MS) is a neurological chronic disease starting in young adulthood. There is no cure but several disease-modifying therapies (DMTs) are used to reduce occurrence of relapses and delay disability progression. In recent years, a number of novel and increasingly effective DMTs have been approved [1](. The availability of new treatment options for MS provides an opportunity for improving tolerance, drug adherence, quality of life and long-term clinical outcomes but it also makes patient management more complex. When choosing a drug, neurologists should take into consideration several parameters including patient and disease characteristics, mechanisms of action, effectiveness, safety profile, way of administration, pregnancy desire and patient preferences. For instance, first-generation immunomodulators (beta interferon and glatiramer acetate – injectable drugs) have well-established short-term and long-term safety profiles, while new oral first-line drugs such as teriflunomide and dimethyl fumarate may appear more convenient from the patient perspective.

Our team recently published a detailed description of the use of DMTs for MS at French national level using the exhaustive MS population issued from the national health data system over 2010-2015 (98% coverage) [2]. First-line DMTs were the mostly used, particularly injectable ones. However, we do expect that therapeutic practices have changed since 2015, as highlighted by another French study using the same database about 10,240 patients initiating a first-line DMT between 2014 and 2016 [3], where oral DMTs had the predominant position (teriflunomide 34.6% and dimethyl fumarate 33.7%). Moreover, based on our previous work on insurance claims data [2], half of patients did not receive any DMT over the 6-year study period while it was estimated to be one third in 2016-2017 in MS expert centers [4]. Such discrepancy can be linked to either data source (i.e. recruitment) or study period (i.e. changes over time) or both.

In that context, we decided to use a large nationwide sample based upon 10-year administrative data to describe time trends in the utilization of DMTs in MS patients in France. The main objective was to describe changes in the use of DMTs over the period 2009-2018, by comparing initial and subsequent DMTs between four successive periods. The secondary objective was to study the impact of the arrival

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of oral DMTs on the use of injectable DMTs, by simulating what would have been the prescriptions without these new drugs.

2. Materials and methods

2.1 Data source

Data were extracted from the General Sample of Beneficiaries ('Echantillon Généraliste des Bénéficiaires', EGB). The EGB database is a representative 1/97 sample of the population (around 600,000 people) covered by the French national healthcare insurance system [5-8]. It contains anonymized demographic characteristics and exhaustive records of healthcare reimbursements including drugs dispensed in retail pharmacies, as well as data on hospital admissions with their related International Classification of Diseases, 10th version (ICD-10) diagnoses.

2.2 Study population

The study population included all patients with MS identified in the EGB database over the study period, i.e. between 1 January 2009 and 31 December 2018. Patients were considered as having MS if they met at least one of the following criteria: (i) having at least one reimbursement for an MS-specific DMT (beta-interferon, glatiramer acetate, fingolimod, natalizumab, teriflunomide or dimethyl fumarate); (ii) having a long-term disease (LTD) registration for MS, or (iii) having at least one hospital admission with a diagnosis of MS based on the ICD-10 G35 diagnosis code [9]. In France, being registered with LTD allows individuals with chronic diseases to receive full healthcare reimbursement. In total, 30 diseases are currently included in the list of LTD, including MS.

The date of MS identification was defined as the earliest date between the date of LTD registration for MS (can be before 2009), the first date of hospitalization for MS or the first date of MS-specific DMT prescription from 2009 to 2018. Based upon data availability, study entry was set at respectively 1 January 2009 for prevalent cases (i.e. MS identified through LTD registration before 2009) and date of MS identification for incident cases (2009-2018). The follow-up period ended with death or the study end on 31 December 2018, whichever came first.

2.3 Data

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Patients with MS were defined as treated if they had at least one reimbursement of the following drugs: beta-interferon, glatiramer acetate, fingolimod, natalizumab, teriflunomide, dimethyl fumarate, azathioprine, methotrexate, mycophenolate mofetil or rituximab. These last 4 drugs were not considered to identify MS cases as they are not MS-specific. Neither mitoxantrone, nor cyclophosphamide and alemtuzumab were considered since they were not available in the hospital data. Neither ocrelizumab nor cladribine or ozanimod were available in 2018 in France.

Demographic patient characteristics included gender, age at MS identification, LTD status (for MS and for other conditions), follow-up duration from MS identification, and occurrence of death. As cause of death was not available in the dataset, for in-hospital deaths, the diagnosis of the hospital stay was used to approximate cause of death.

Molecules and start/stop dates from drugs claims were considered to describe therapeutic management of MS. Initial DMT and subsequent ones were considered. DMTs were also classified into four groups: first-line injectable (beta-interferon and glatiramer acetate), first-line oral (dimethylfumarate and teriflunomide), second-line (natalizumab and fingolimod), and off-label (azathioprine, methotrexate, mycophenolate mofetil and rituximab). Untreated periods were also considered in the analyses, and defined as a minimum of 3 months without any drug claim.

Four periods of MS identification were defined (before 2009, 2009 to 2011, 2012 to 2015 and 2016 to 2018), in order to assess changes in MS therapeutic management. For prevalent cases (identified before 2009), age at study entry and age at MS identification were computed, while for incident cases (from 2009 to 2018), study entry always corresponded to MS identification.

2.4 Statistical analysis

Characteristics of patients and DMTs use were described from study entry, overall and for each time period. The time from study entry to death was calculated using Kaplan-Meier estimates [10]. Characteristics of patients who took at least one DMT and characteristics of patients who did not receive any DMT over the study period were also described overall and for each time period. Prescriptions of each DMT were computed for each patient from study entry on a monthly basis and summarized in a chronogram. Such graph displays the overall pattern of therapeutic use, with the cumulative proportion

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of patients per DMT (y-axis) for each time unit (x-axis). In addition, therapeutic sequences, i.e. initial drug and subsequent ones, were represented using sunburst diagrams, as such graphs make possible to visualize hierarchical data, depicted by concentric circles. The circle in the centre represents the root node (the initial DMT in the present case), with the hierarchy moving outward from the center (subsequent DMTs).

Then, time series of each DMT from January 2009 until February 2014 (first first-line oral drug availability) were used to forecast trends from March 2014 to December 2018, to simulate what would have happened in the absence of new marketed oral drugs. For that purpose, a seasonal autoregressive integrated moving average (SARIMA) model [11] was implemented. The component models were fitted independently on the training period and then used to forecast the expected numbers over the test period. For each component model, 80% prediction intervals were estimated based on the standard deviation of each step forecast [12].

Regarding comparisons according to time periods, as theoretical follow-up duration decreased over time, several indicators were calculated on a duration truncated to two years, in order to make them comparable.

All analyses were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) except time series analyses which were performed using the fpp2 library [12] of the R version 3.6.1 software [13].

3. Results

3.1 Characteristics of the study population

In the EGB sample which represents 1/97 of the whole French health insurance database, 1,508 patients were identified as having MS over the period 2009-2018. Almost half of the patients (48.9%, n=738) were identified before 2009 (prevalence rate: 129 per 100,000) as they presented a LTD status for MS, and the remaining were incident cases over the study period. Indeed, 15.6% (n=236) were identified between 2009 and 2011, 20.9% (n=315) between 2012 and 2015 and 14.5% (n=219) between 2016 and

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2018. Characteristics of the overall study population as well as subgroups according to periods of MS identification are presented in Table 1A. Median age at MS identification was 41 years and 70.2% of patients were women. Among prevalent cases, age at study entry was 49 years while age at MS identification was 39 years. Overall, one third of patients with MS had another long-term disease status, reflecting the burden of comorbidities. In addition, 10.7% of patients died over the median follow-up duration of 9 years. Among the 161 deaths, median age at death was 69 years, and 29.8% occurred at hospital; the medical diagnosis of this stay was MS in 77.1% of them. Moreover, 50.9% of the deceased patients (n=82) had at least another LTD status, cardiovascular diseases (n=58) and cancer (n=33) being the most common.

3.2 Comparison of treated with untreated patients

Overall, 876 patients (58.1%) were treated at least once over the study period. As shown in Table 1B, treated patients were younger than untreated patients. As expected, LTD registration for MS was more frequent among treated patients than untreated patients while LTD registration for another disease was higher among untreated patients, probably reflecting older age and comorbidities. In accordance, the crude survival probability was higher in patients who received at least one DMT over the study period than in untreated ones (Figure 1).

3.3 Use of DMTs over time

Use of DMTs over time is described on Figure 2 where monthly proportions of patients per DMT are presented. About two-thirds of patients were not treated each month and this proportion was stable over time. These repeated cross-sectional proportions have to be confronted with the proportion of patients who were never treated on the 10-year period, i.e. 41.9% (Table 1B).

The use of the new oral treatments as soon as they arrived was clear, with fingolimod from 2011 (orange) and dimethyl fumarate and teriflunomide from 2014 (light-blue). Marketing of the two first-line oral drugs has led to a large decrease in the use of first-line injectable drugs, especially beta-interferon (dark-blue), while second-line and off-label drugs did not seem to be impacted. At the end of the study period,

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it should be noted that all products seemed to share almost equal parts (beta interferon, teriflunomide, dimethyl fumarate, and fingolimod, then natalizumab and glatiramer acetate).

This shift to new marketed drugs was confirmed using the time-series model, as shown in Figure 3, when comparing the expected prescriptions (dotted lines) to the actual ones (solid lines) on the period 2014-2018.

3.4 Therapeutic sequences over time

Additional characteristics of longitudinal therapeutic sequences are summarized in Table 2 and Figure 4. Initial DMT was mostly first-line DMTs (around 75-80%), followed by off-label (around 10-15%) and second-line DMTs (around 10%). Nearly half of patients switched from initial DMT to another DMT over the follow-up, and when restricting follow-up duration to the first two years, the proportion of patients receiving more than one DMT seemed to increase from ancient periods to more recent periods. In 2012-2015, the proportion rose to 27.6%, probably linked to the arrival of oral first-line drugs. Overall, 24.3% of patients received a second-line DMT, without period effect.

Sunburst diagrams (Figure 4) showed the variety of therapeutic sequences, overall and in each time period. Indeed, many patients received different kinds of DMTs, as represented by the different colors in the concentric bands. Here again, the shift from injectable to oral first-line drugs was clear over time. By contrast, use of second-line DMTs (in red) either in escalating strategy or as initial treatment seemed stable over time. We can notice that patients also regularly underwent discontinuation of DMTs (in yellow).

4. Discussion

The present study aimed to describe temporal trends in therapeutic management of MS in France over the period 2009-2018. As expected, we showed that patients were treated earlier over time and many of them received several DMTs. Moreover, in the past 10-year period, it seems that as soon as a drug becomes available, it is used to the detriment of previous ones, leading to a strong shift from injectable to oral first-line DMTs over time.

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The data were based on a representative 1/97 random sample of the French population covered by the health insurance system (98%), which reduces selection bias and offers the opportunity to describe the wide MS population. The characteristics (e.g. gender, age, and LTD status) of the study population are very close to those of MS patients in France in general [14].

Overall, our results are in line with a recent Canadian descriptive study [15] where people who were not treated during follow-up were older and had a higher comorbidity burden than people who were treated. Nonetheless, it can be noticed that nearly 1 in 4 treated patients had at least some comorbidity, and/or were 50 years or older.

Our results regarding DMTs use are also consistent with those previously published about DMT initiations in 2016-2018 [3]. Indeed, we found that the proportion of patients treated with beta interferon (initiations and follow-up) decreased by half when new oral drugs became available. At the end of the study period, relative parts of each first-line DMT were almost similar. Our results are also in accordance with a French nation-wide study based upon the insurance regimen dedicated to self-employed workers (6% of the French general population) which found an overall DMT utilization of 34% in 2013 and 38% in 2015 [16]. They also showed that the first-generation DMT utilization rate decreased to the profit of second-generation drugs.

We also showed that about two-thirds of patients with MS were not treated each month, and 41.9% were never treated during the 10-year period. It should be noted that never treated patients in the present study do not necessarily correspond to patients who never received DMT throughout the whole disease course, as the term “never” only refers to the limited observation period, i.e. 2009-2018. Such estimates are consistent with annual untreated proportions of 66% and 61% in 2013 and 2015, respectively [16], but are higher than the 31% of patients from MS expert centers who were not receiving a DMT in 2016-2017 [4]. When looking at international literature, 29% of MS cases filled a DMT prescription in Canada during the 22-year study period [15], 10% to 50% in Denmark depending on MS onset period [17], half of patients enrolled in a private health insurance program versus one third of those enrolled in a public program in the US [18] and 80% in MSBase [19]. The differences in the proportions of untreated between studies likely reflect differences in patients’ selection (age, MS phenotype, health status…), study period, and healthcare systems. Indeed, use of DMT was generally higher in the more recent

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periods in line with the increased availability of drugs, as well as in patients selected from MS expert centers, such as OFSEP [4] or MSBase [19] series. In population-based studies ([15;17]; the present one), there is no recruitment bias, which may represent a significant advantage over recruitment through MS centers which focus on patients who are actively seeking expert care and may led to more severe MS patients [20]. In France, DMTs are fully reimbursed by the health insurance system, which is not the case in many countries. We could assume that the absence of personal expense (out-of-pocket cost) should facilitate access to treatment, but obviously, it does not mean that the proportion of untreated patients is decreased. As the untreated subgroup was found to be older than the treated one, it probably included patients with progressive MS, but information related to MS phenotype was not available in the present dataset.

Among treated patients, we also found regular periods without treatments which may reflect different situations: treatment discontinuation due to side effects, treatment discontinuation before and/or during pregnancy, washout period required when switching from one agent to another, other personal reasons (convenience, lassitude, travel…). This was also highlighted in patients coming from MS expert centers, where treatment exposure was only 60% of total follow-up [4].

The variety in therapeutic sequences is in line with findings previously published by our team [2] and illustrates both the lack of clear and specific recommendations in France and the shared indications among drugs. It also reflects the increased number of available drugs, as well as the expanding literature about the comparative effectiveness and safety in real-word settings, and therapeutic strategies. Overall, half of patients were exposed to only one DMT over follow-up, nearly 80% of people filled a prescription for a first-line DMT and one quarter for a second-line DMT.

In the last 20 years, the treatment options for relapsing-onset MS have considerably been enriched with a variety of new drugs in order to reach a better control of the disease. In that context, neurologists are asked to initiate effective treatment early in the disease course, monitor treatment response, and modify or switch therapies in case of failure. We can assume that the level of expectations regarding disease control is increasing from both neurologists and patients, and that a new goal of "no evidence of disease activity" (NEDA) may be supplanting the previous aim of relapse rate reduction [21]. However, in the

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present work, we were not able to measure effectiveness of the therapeutic strategies, as our main limitation was the lack of clinical data. Indeed, we observed therapeutic practices from French neurologists and changes over time, but we cannot assess whether the DMT choices were appropriate, whether switch decisions were done at the right time, or whether untreated patients did really not need to be treated, as we did not have information regarding relapses, disability, MRI parameters. Even MS phenotype was not available, meaning that we could not stratify findings between relapsing and progressive forms. In addition, the last period of MS identification (2016-2018) was probably too short to reflect current practices. However, such descriptive real-world studies can offer the opportunity to describe use of DMTs in subpopulations that are generally excluded from randomised clinical trials, such as old patients or late-onset MS or pregnant women.

To conclude, the present work offers an overview of real-world DMT exposure patterns in patients with MS and shows how the therapeutic practices have changed over time in France, in relation to new marketed drugs. In our opinion, such cross-sectional and longitudinal descriptions are worth being done regularly, in order to get reference population-based data regarding therapeutic management of MS in a universal care setting.

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Figures Legend

Figure 1. Crude survival probabilities of patients treated at least once versus untreated patients over the study period (n=1,508)

Figure 2. Use of disease modifying therapies (DMTs) in patients with multiple sclerosis over the period from 2009 to 2018 in France (n=1,508)

Figure 3. Trends in the use of disease modifying therapies (DMTs) in patients with multiple sclerosis over the period from 2009 to 2018 (n=876)
(Observed values (solid lines) from 2009 to 2014 and predicted values (dotted lines) with 80% confidence intervals from 2014 to 2018)

Figure 4. Therapeutic sequences from the first treatment initiation observed in patients with multiple sclerosis over the study period (n=876), overall and according to periods of multiple sclerosis (MS) identification

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Table 1A. Characteristics of the study population, overall and according to periods of multiple sclerosis (MS) identification (n=1,508)

Period of MS identification	**Overall cohort** **N=1,508**	**Before 2009** **n=738 (48.9%)**	**2009-2011** **n=236 (15.6%)**	**2012-2015** **n=315 (20.9%)**	**2016-2018** **n=219 (14.5%)**
Women, n(%)	1,058 (70.2%)	540 (73.2%)	155 (65.7%)	218 (69.2%)	145 (66.2%)
Age at MS identification (years)*	41 (32-50)	39 (31-48)	43 (34-54)	40 (30-51)	43 (32-53)
Age at study entry (years)*	45 (36-57)	49 (40-59)	43 (34-54)	40 (30-51)	43 (32-53)
Time from MS identification in 2009 (years)*	0 (0-8)	8 (4-13)	--	--	--
Long-term disease for MS at entry, n(%)	1.278 (84.7%)	738 (100.0%)	162 (68.6%)	222 (70.5%)	157 (71.7%)
Age at LTD for MS registration (years)*	40 (31-48)	39 (31-48)	42 (33-49)	39 (30-48)	42 (31-49)
At least another LTD over the study period, n(%)	509 (33.8%)	229 (31.0%)	97 (41.1%)	111 (35.2%)	72 (32.9%)
Follow-up time (years)*	9 (4-10)	10 (10-10)	9 (8-9)	5 (4-6)	2 (1-2)
Deaths over the study period, n(%)	161 (10.7%)	104 (14.1%)	33 (14.0%)	21 (6.7%)	3 (1.4%)

*median (q1-q3); MS: Multiple Sclerosis, LTD: Long-Term Disease.

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Table 1B. Characteristics of patients treated at least once and untreated patients over the study period, overall and according to periods of multiple sclerosis (MS) identification (n=1,508)

Period of MS identification	Overall cohort N=1,508		Before 2009 n=738 (48.9%)		2009-2011 n=236 (15.6%)		2012-2015 n=315 (20.9%)		2016-2018 n=219 (14.5%)	
	Treated n=876 (58.1%)	Not treated n= 632 (41.9%)	Treated n=429 (58.1%)	Not treated n=309 (41.9%)	Treated n=134 (56.8%)	Not treated n=102 (43.2%)	Treated n=196 (62.2%)	Not treated n=119 (37.8%)	Treated n=117 (53.4%)	Not treated n=102 (46.6%)
Women, n(%)	619 (70.7%)	439 (69.5%)	319 (74.4%)	221 (71.5%)	88 (65.7%)	67 (65.7%)	133 (67.9%)	85 (71.4%)	79 (67.5%)	66 (64.7%)
Age at MS identification (years)*	38 (29-45)	46 (36-58)	37 (30-44)	43 (35-51)	40 (31-45)	53 (41-65)	36 (29-46)	49 (37-65)	39 (30-47)	49 (35-60)
Age at study entry (years)*	42 (33-49)	54 (43-63)	45 (37-54)	56 (46-64)	40 (31-45)	53 (41-65)	36 (29-46)	49 (37-65)	39 (30-47)	49 (35-60)
LTD for MS at entry, n(%)	817 (93.3%)	461 (72.9%)	429 (100.0%)	308 (99.7%)	118 (88.1%)	44 (43.1%)	171 (87.2%)	51 (42.9%)	99 (84.6%)	58 (56.9%)
At least another LTD, n(%)	232 (26.5%)	277 (43.8%)	111 (25.9%)	118 (38.2%)	43 (32.1%)	54 (52.9%)	53 (27.0%)	58 (48.7%)	25 (21.4%)	47 (46.1%)
Follow-up time (years)*	10 (5-10)	8 (3-10)	10 (10-10)	10 (10-10)	9 (8-10)	8 (7-9)	5 (4-6)	4 (4-6)	2 (1-3)	1 (1-2)
Deaths over the study period, n(%)	40 (4.6%)	121 (19.1%)	27 (6.3%)	77 (24.9%)	8 (6.0%)	25 (24.5%)	5 (2.6%)	16 (13.4%)	0 (0.0%)	3 (2.9%)

*median (q1-q3); MS: Multiple Sclerosis, LTD: Long-Term Disease.

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Table 2. Characteristics of the use of disease modifying therapies (DMTs) in patients with multiple sclerosis who were treated at least once over the study period (n=876)

	Overall cohort n= 876 (100.0%)	Before 2009 n=429 (49.0%)	2009-2011 n=134 (15.3%)	2012-2015 n=196 (22.4%)	2016-2018 n=117 (13.4%)
Age at first DMT (years)*	43 (34-51)	46 (39-55)	41 (33-47)	36 (30-46)	40 (30-47)
Time from study entry to first DMT (months)*	3 (1-13)	1 (0-23)	5 (1-15)	4 (2-11)	2 (1-5)
Treated in the 2 years following study entry, n(%)	730 (48.4%)	327 (44.3%)	109 (46.2%)	177 (56.2%)	117 (53.4%)
First DMT prescribed over the study period, n(%)					
Beta interferon	365 (41.7%)	207 (48.3%)	75 (56.0%)	61 (31.1%)	22 (18.8%)
Glatiramer acetate	162 (18.5%)	83 (19.3%)	27 (20.1%)	31 (15.8%)	21 (17.9%)
Teriflunomide	74 (8.4%)	15 (3.5%)	6 (4.5%)	27 (13.8%)	26 (22.2%)
Dimethyl fumarate	70 (8.0%)	5 (1.2%)	4 (3.0%)	36 (18.4%)	25 (21.4%)
Natalizumab	32 (3.7%)	13 (3.0%)	1 (0.7%)	13 (6.6%)	5 (4.3%)
Fingolimod	44 (5.0%)	25 (5.8%)	4 (3.0%)	11 (5.6%)	4 (3.4%)
Azathioprine	45 (5.1%)	30 (7.0%)	7 (5.2%)	4 (2.0%)	4 (3.4%)
Methotrexate	41 (4.7%)	32 (7.5%)	4 (3.0%)	3 (1.5%)	2 (1.7%)
Mycophenolate mofetil	29 (3.3%)	14 (3.3%)	5 (3.7%)	7 (3.6%)	3 (2.6%)
Rituximab	13 (1.5%)	4 (0.9%)	1 (0.7%)	3 (1.5%)	5 (4.3%)
Number of DMTs per patient in the first two years of follow-up >=2, n(%)	156 (17.8%)	59 (13.8%)	23 (17.2%)	54 (27.6%)	20 (17.1%)
Type of DMT: at least one, n(%)					
First-line	688 (78.5%)	319 (74.4%)	112 (83.6%)	159 (81.1%)	95 (81.2%)
Injectable	549 (62.7%)	298 (69.5%)	104 (77.6%)	103 (52.6%)	44 (37.6%)
Oral	317 (36.2%)	103 (24.0%)	50 (37.3%)	101 (51.5%)	63 (53.8%)
Second-line	213 (24.3%)	107 (24.9%)	36 (26.9%)	56 (28.6%)	14 (12.0%)
Off-label use	167 (19.1%)	109 (25.4%)	22 (16.4%)	21 (10.7%)	15 (12.8%)
DMTs including non MS-specific, n(%)					
Beta interferon	404 (46.1%)	228 (53.1%)	83 (68.6%)	69 (35.2%)	24 (20.5%)
Glatiramer acetate	204 (23.3%)	101 (23.5%)	37 (30.6%)	44 (22.4%)	22 (18.8%)
Teriflunomide	176 (20.1%)	72 (16.8%)	27 (22.3%)	46 (23.5%)	31 (26.5%)

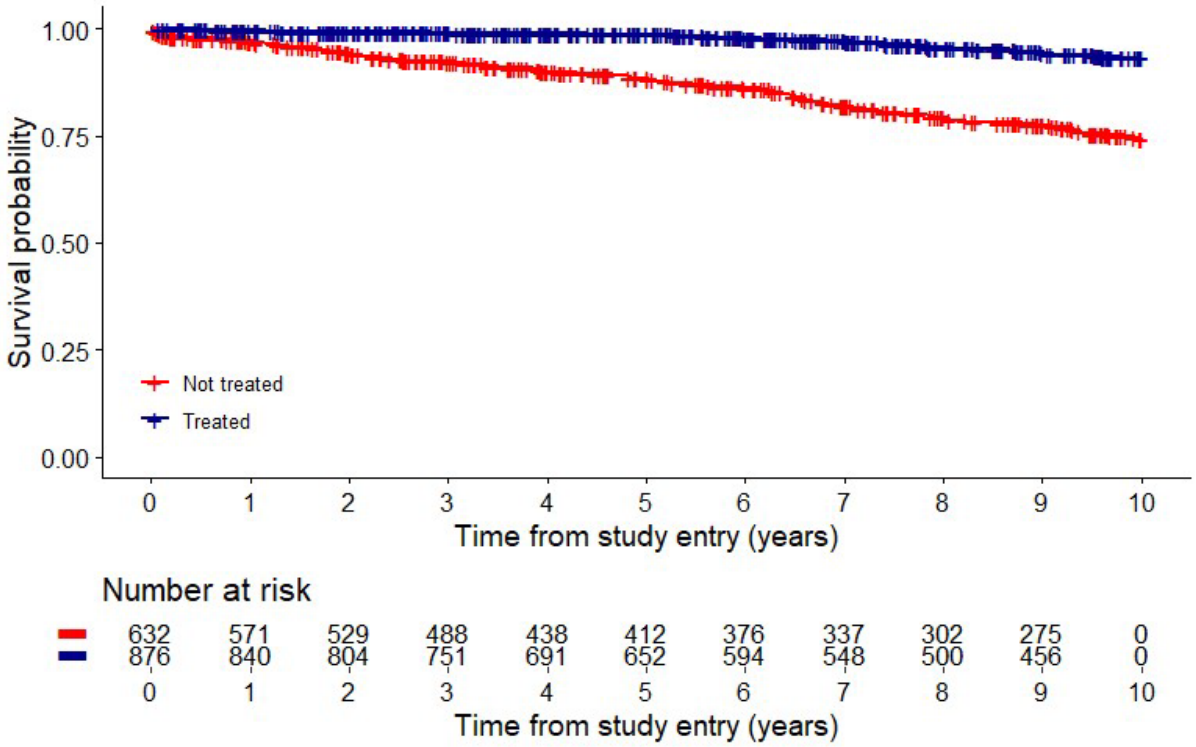
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Dimethyl fumarate	176 (20.1%)	46 (10.7%)	30 (24.8%)	63 (32.1%)	37 (31.6%)
Natalizumab	110 (12.6%)	64 (14.9%)	13 (10.7%)	27 (13.8%)	6 (5.1%)
Fingolimod	139 (15.9%)	71 (16.6%)	25 (20.7%)	35 (17.9%)	8 (6.8%)
Azathioprine	59 (6.7%)	38 (8.9%)	9 (6.7%)	7 (3.6%)	5 (4.3%)
Methotrexate	53 (6.1%)	44 (10.3%)	4 (3.0%)	3 (1.5%)	2 (1.7%)
Mycophenolate mofetil	41 (4.7%)	21 (4.9%)	9 (6.7%)	8 (4.1%)	3 (2.6%)
Rituximab	31 (3.5%)	16 (3.7%)	3 (2.2%)	5 (3.6%)	7 (6.0%)
Follow-up proportion under treatment (%)*	82 (37-96)	81 (35-99)	82 (38-95)	85 (51-94)	76 (52-89)

*median (q1-q3); MS: Multiple Sclerosis; DMT: Disease Modifying Therapy.

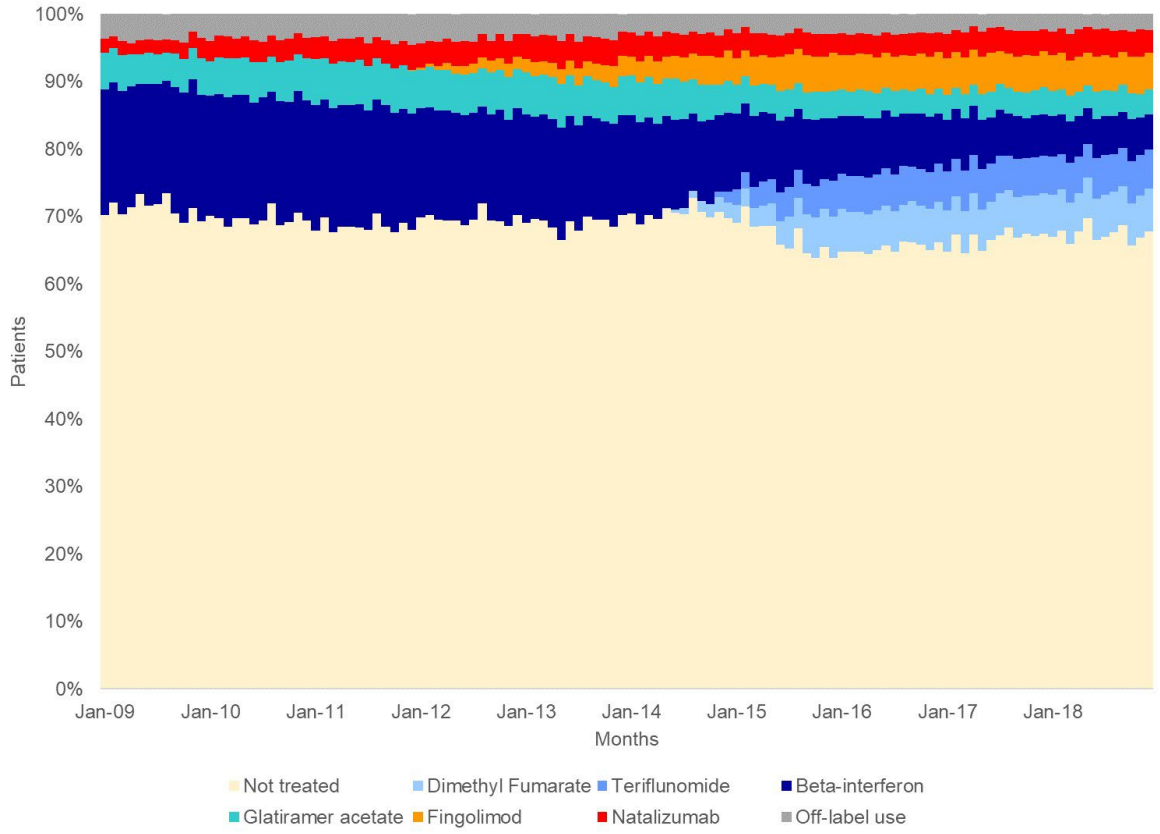
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Fig1



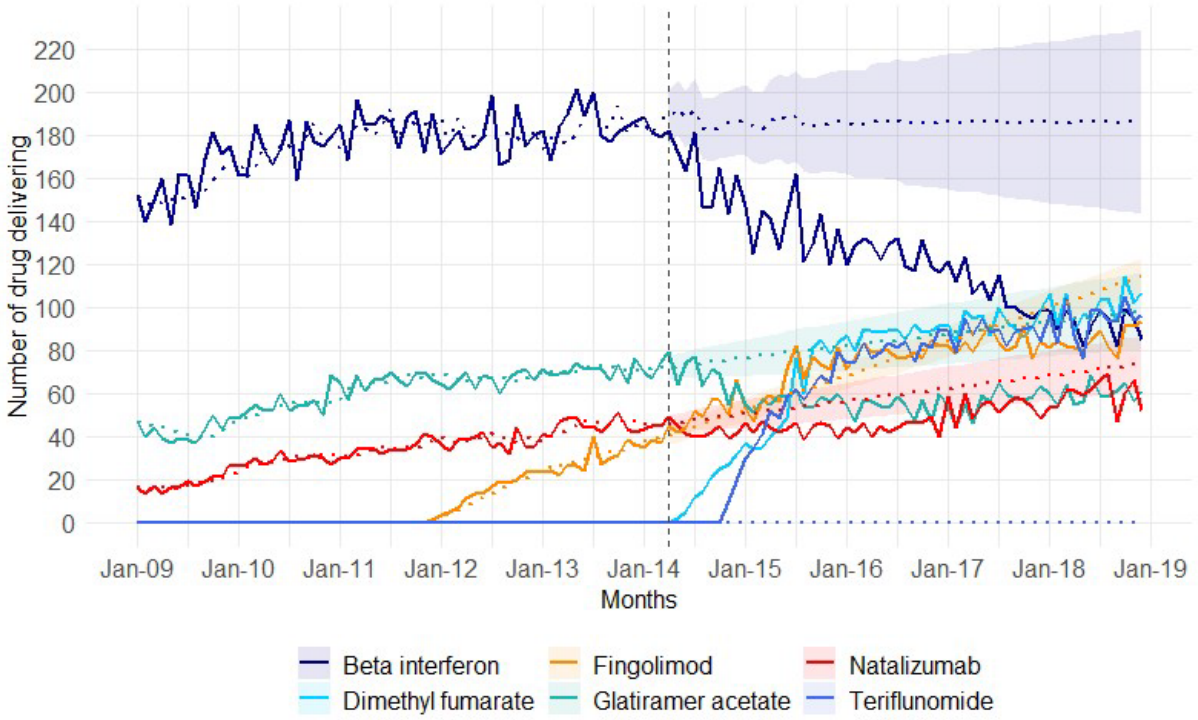
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Fig2



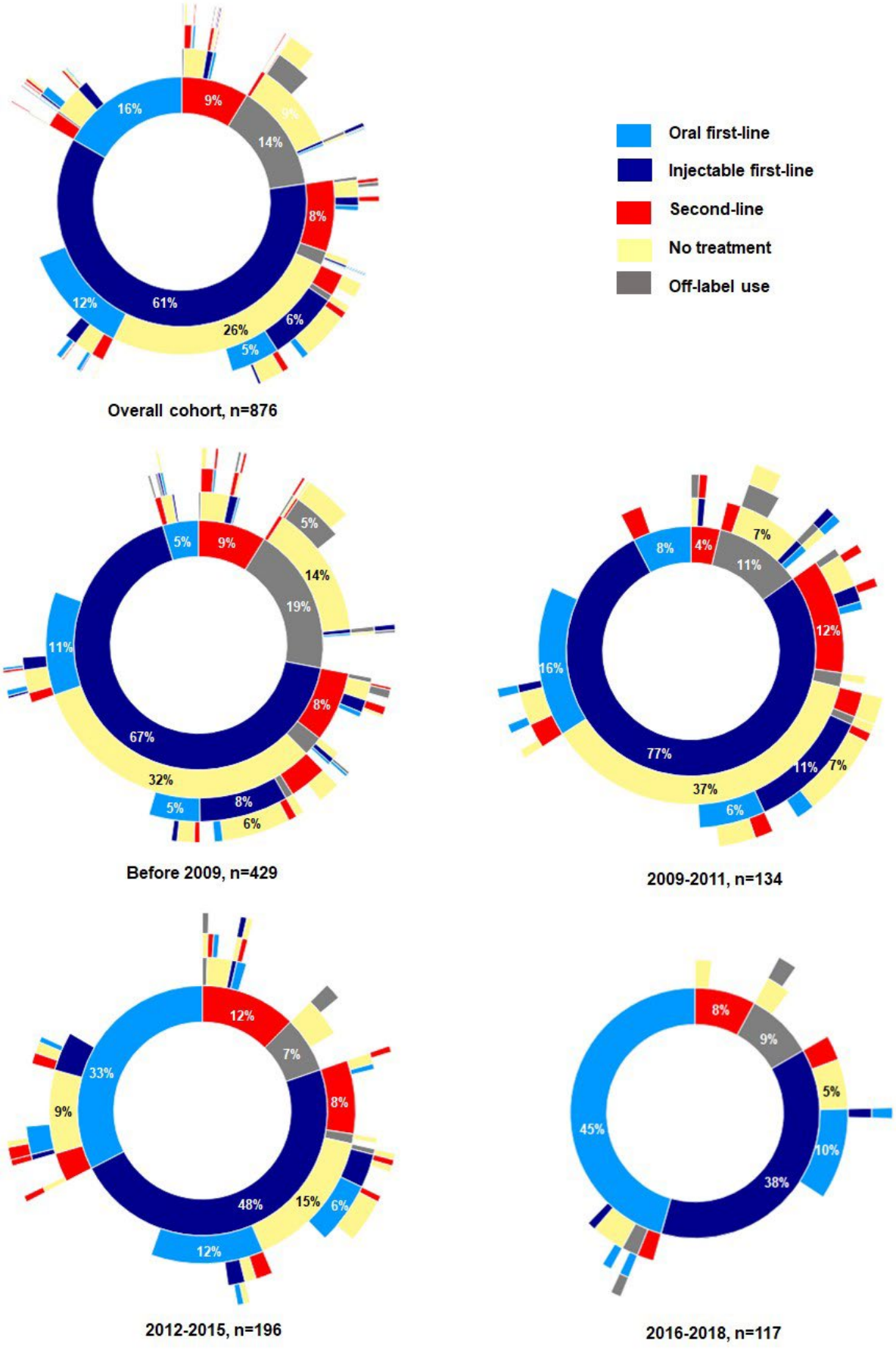
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Fig3



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Fig4



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