

Epidemiology and therapeutic management of highly active relapsing-remitting multiple sclerosis adults in the French national health insurance database

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Abstract

Background: In France, no specific information on the Highly Active Relapsing-Remitting Multiple Sclerosis (HA-RRMS) population is available.

Objective: To describe the epidemiology and therapeutic management of HA-RRMS patients in France.

Methods: In this cohort study, HA-RRMS patients were identified in the health data system with a new algorithm using outpatient healthcare consumption and hospital discharge data.

Results: Over 2010–2015, 9,596 incident HA-RRMS patients were identified (sex ratio: 2.8; mean age 39.9 years old) and followed-up for 4.0 years, on average. In 2015, the incidence and mortality rates in patients aged 20 and above were 3.6 and 389 per 100,000, respectively (lower mortality than in the MS population but twice as high as in the French population). During the study, 39.7% of patients took a disease-modifying drug (DMD) and 83.5% a high efficacy DMD (HE-DMD, fingolimod or natalizumab, with a mean treatment duration of 3.5 years). When patients treated by an HE-DMD required to switch to another treatment, it was more often to the other HE-DMD (more often from natalizumab to fingolimod) than to a DMD.

Conclusions: According to this first real-world study, HA-RRMS patients could represent 8% of MS patients. The results validated the algorithm to identify HA-RRMS patients.

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, neurodegenerative disorder of the central nervous system. It is the leading cause of non-traumatic neurological disability in young adults in the USA and Europe.¹ Over 2010–2015, about 110,000 persons had MS in France.²

MS is classified into relapsing or progressive forms, with Relapsing-Remitting MS (RRMS) accounting for 85% of all initial diagnoses. RRMS is characterized by intermittent disease relapses followed by periods of remission. Over time, 80% of patients with RRMS progress to secondary progressive MS, characterized by an accumulation of permanent disability without significant relapses or remissions. In some cases, the disease may be a progressive accumulation of disability from onset (primary progressive MS).^{3,4} There is yet a group of patients which remains difficult to define and for which there is no consensus about their treatment.^{5,6} These patients have frequent relapses and/or Magnetic Resonance Imaging (MRI) activity (either when untreated or while on a Disease-Modifying Drug [DMD] therapy) and have what might be termed as a Highly Active RRMS (HA-RRMS).^{6,7}

Several DMDs have been approved for the treatment of MS over the last 20 years.⁸ Although no cure for MS exists, current treatments aim to reduce the frequency and severity of relapses, while preventing disability progression.⁹ These therapies, such as interferons β and glatiramer acetate, teriflunomide and dimethyl-fumarate are available for MS. At the time of the study, for patients with active disease and an

insufficient response to at least one drug, as well as for patients with rapidly evolving severe RRMS, two immunosuppressants called high efficacy DMD (HE-DMD) had approval for use in France. These HE-DMDs, natalizumab and fingolimod, became available in France in 2007 and December 2011, respectively.

Several studies have been conducted on the French National Health Insurance (NHI) database to characterize the whole MS population through several identification algorithms.^{2,10} However, none of these studies described HA-RRMS patients, whose disease management is more complex and still being debated.¹¹ Furthermore, most of these studies had a short follow-up period (1 year). Therefore, a national-level retrospective cohort study was set up, using NHI data, to describe incident HA-RRMS adult patients living in France, over 2010–2015, and their disease management, and followed them up until 2017.

Methods

Study design

We performed a longitudinal retrospective cohort study based on the National Health Data System (SNDS) from the NHI, and specifically, on data extracted from the SNIIRAM (Système National d'Information Inter-Régimes de l'Assurance Maladie) database.

Patients were included in the study on an index date. The index date was defined as either the date of the first reimbursement of HE-DMDs or the date of relapse, during the inclusion period (January 1st, 2010 to December 31st, 2015). Patients were followed until criteria were met (death, one year without any medical care expenses, end of the study (December 31st, 2017)), whichever occurred first. Hence, patient follow-up lasted up to seven years. Data was extracted between January 1st, 2008 (to allow for the identification of HA-RRMS patients) and December 31st, 2017.

Data sources

The SNIIRAM is briefly described in Supplement 1 and in detail elsewhere.¹² In short, it contains comprehensive, individual-level, anonymized data on all healthcare expenses reimbursed by the French NHI. The NHI covers primary and secondary care expenses, medications, medical devices, and hospital costs¹³ (additional information in Supplement 2). The General Scheme, covering 76% of inhabitants, is the largest scheme of the NHI.

Study population

We included adults (≥ 18 years) continuously affiliated to the General health insurance Scheme between two years prior to the index date and 2017. According to an algorithm developed with two neurologists, HA-RRMS patients were included when meeting at least one of the following criteria:

1) Treatment criterion: At least one reimbursement of the only two available HE-DMD in France for HA-RRMS (natalizumab, fingolimod);

2) Relapse criterion: At least two relapses in one year and no previous treatment for MS during the previous two years and an MRI of the central nervous system performed during the three months following the 2nd relapse and a DMD during the six months following the MRI;

3) Relapse criterion: One relapse in one year despite a DMD, with an MRI of the central nervous system performed during the three months following the relapse and a switch of DMD during the six months following the MRI.

Relapses were defined using a validated US claims-based algorithm¹⁴ and were adapted to French clinical practice: 1) A hospitalization with a principal diagnosis (PD) of MS (PD with International Classification of Disease 10th revision G35 “Multiple sclerosis”), excluding hospitalization for administration of MS treatment (PD Z51.2 and related diagnosis [RD]/significant associated diagnosis [SAD] G35), for a surgery disease-related group (GHM [Groupe Homogène de Malades]) or a GHM with botulinum toxin injection; 2) And/or a hospital or outpatient neurologist visit in addition to an oral or intravenous corticoid reimbursement within 15 days of the visit.

Relapse events that occurred within the same 30-day period were treated as a single relapse. Exclusion criteria are listed in Supplement 3.

New HA-RRMS patients were defined as patients without reimbursement for HE-DMDs and/or without MS relapse(s) twelve months prior to the index date. HE-DMD discontinuation was defined as three months without natalizumab infusion or three months after end of last dispensed fingolimod tablets. Discontinuation for pregnancy was defined by the occurrence of a delivery within fifteen months after treatment discontinuation. Switch of DMD or HE-DMD was defined as dispensing of the alternative DMD or HE-DMD six months following the date of discontinuation of the initial treatment.

Outcomes of interest

Baseline characteristics of the study population (demographic data, comorbidities, long-term disease (LTD) status, disability pension) and therapeutic management (drugs [Supplement Table 1], hospitalizations [Supplement 4], primary and secondary care, laboratory tests, imaging procedures, transportation, medical devices, and date of care) were collected. Of note, all secondary care visits accounted for were those held in the community and not at the hospital; all hospital practitioners' visits were combined together.

Statistical analyses

Continuous, quantitative variables were summarized with the number of patients (n), mean, and standard deviation (SD). Categorical, qualitative variables were summarized with the percentage of patients per category. Confidence intervals were computed using the normal approximation. The definition of HA-RRMS prevalence, incidence, mortality and the Charlson Comorbidity Index are in Supplement 5.

Treatment duration was assessed with the Kaplan-Meier method. The SNIIRAM covers almost the entire French population,¹² thus no sample size calculation was necessary.

Ethics

Patient consent was not necessary because this study uses secondary data and protection of patients' rights and freedom were guaranteed by the French data protection authority (CNIL: decision DR-2018-099). Study protocol was approved by the committee for research, studies and evaluations in the field of health (CERES) and all methods were performed in accordance with the corresponding guidelines. STROBE cohort reporting guidelines¹⁵ were used.

Results

Study population characteristics

Over 2010–2015, 12,830 HA-RRMS adult prevalent patients were included in the study, of which 12,820 (72.0%) were identified in the database through drug use (criterion 1), 250 (1.4%) and 4,981 (27.6%) through relapses (criteria 2 and 3, respectively) (supplement Fig. 1). Among the prevalent patients, 9,596 were incident patients (6,704 with criterion 1 [69.9%], 173 with criterion 2 [1.8%], and 2,719 with criterion 3 [28.3%]). Incident patients were followed-up for a mean duration of 4.0 years, corresponding to 38,394 patients-years. Finally, 8,045 incident patients (83.8%), 3,167 (33.0%) and 961 (10.0%) were followed for at least 2, 5 and 7 years, respectively.

Almost $\frac{3}{4}$ of incident patients were women (7,067 women, 73.7%) and the mean age at index date was 39.9 years old (SD 10.5, median 39.0) (Table 1). Most patients had obtained LTD status (9,539 patients, 99.4%), and 45.6% (4,352 patients) of those with an LTD status got it within five years prior to their index date. Over the study period, 6,646 (69.3%) incident patients had a Charlson Comorbidity Index of 0 and 632 (6.6%) had an index of 3 or above. Of the 9,238 incident patients under the age of 60, 1,835 (19.1%) had a disability pension at index date. Most of them (1,153 patients, 62.8%) had a level 2 disability pension. When considering the first change in pension level over the study period, 1,863 (20.2%) had an increase and 126 (1.4%) a decrease in pension level. Among the patients with an increase to level 2 or 3 disability pension, the change occurred, on average, after 6.4 years.

During the study, on average, incident patients experienced 1 (SD 2.0) relapse every other year. Criterion 1, 2 and 3 patients had 0.04 relapse/year (SD 0.2), 1.0 relapse/year (SD 0.8) and 1.7 relapse/year (SD 1.3), respectively.

Epidemiology

Among adults 20 years old and above, the age-standardized prevalence rate increased from 11.0 HA-RRMS cases per 100,000 in 2010 to 26.5 HA-RRMS cases per 100,000 in 2015 (Table 2). The age-standardized incidence rate was 3 new cases per 100,000 in 2010. It increased up to 4.5 new cases per

100,000 in 2012, then remained above 3.6 case per 100,000 until 2015. Between 2010 and the end of the study follow-up in 2017, 122 HA-RRMS patients over 20 died (4 patients aged 18 to 20) and the crude mortality rate varied between 113 deaths per 100,000 HA-RRMS patients in 2010 and 389 deaths per 100,000 HA-RRMS patients in 2015 (Table 3). The mortality rate of HA-RRMS patients was significantly about twice as high as the mortality rate of the French population in 2011, 2014 and 2015.

Disease management

Drugs

Within the two years prior to the index date, 7,202 (75.0%) patients had taken a DMD (Table 4). During the study follow-up, 3,809 patients (39.7%) took a DMD; interferon beta was again the most common DMD (22.6% of patients treated) (Table 5). At index date, 6,704 (69.9%) patients were taking an HE-DMD (fingolimod [38.8%] and natalizumab [31.1%]) (Fig. 1). Patients took HE-DMDs (initiated at index date or later) for, on average, 3.5 years prior to discontinue it. This includes 225 women who stopped HE-DMDs and gave birth; 190 (84.4%) of them restarted an HE-DMD after childbirth. During the study, 32.5% of patients treated with natalizumab at index date switched to fingolimod, after a mean treatment duration of 4.2 years. Conversely, 7.0% of those treated with fingolimod at index date switched to natalizumab, after a mean treatment duration of 3.5 years. About a third of patients (32.8%, 1,926 patients out of 5,865) ever treated with fingolimod during the study discontinued their treatment and 63.5% (2,328 out of 3,664 patients) ever treated with natalizumab discontinued their treatment, after a mean treatment duration of 3.5 and 2.7 years, respectively. Of the patients ever treated with fingolimod, 7.4% switched to a DMD and 4.4% to natalizumab (Table 6). Meanwhile, of the patients ever treated with natalizumab, 10.0% switched to a DMD and 27.9% to fingolimod. During the study, 1,308 of 2,892 patients (45.2%) not treated with an HE-DMD at index date initiated an HE-DMD (on average, 4.4 months after the index date). Of those with fingolimod as their first HE-DMD, 102 switched to rituximab and 352 switched to a DMD; of those with natalizumab as their first HE-DMD, 96 switched to rituximab and 305 switched to a DMD. Taken as a whole, 83.5% (8,012 patients) took an HE-DMD during the study.

The following results are based on the 8,045 patients with at least two years of follow-up.

DMD: disease-modifying drug ; HE DMD: High Efficacy disease-modifying treatment (natalizumab, fingolimod). Some patients are present in several boxes and several lines.

Hospitalization, primary and secondary care visits

During the study period, 7,485 patients (93.0%) had at least one MS-related hospitalization (Table 7). The mean annual number of hospitalizations was 4.7 (SD 4.6) and higher during the first year of follow-up (6.3, SD 5.8). During the first year of follow up, almost all patients (7,920 patients, 98.5%) had visited at least once a general practitioner (GP) (Table 8). A large proportion also visited at least once other community-based specialists caring for MS. Throughout the study, patients had, on average, 28.2 (SD 145.2) nurse, 26.0 (SD 37.9) physiotherapist, 8.2 (SD 5.9) GP and 0.8 (SD 1.4) neurologist visits, per year.

Laboratory tests, imaging procedures and medical devices

During the first year of follow up, 6,831 (84.9%) of patients had at least one complete blood count and 4,812 (59.8%) at least one MRI of the central nervous system. On average, 0.9 (SD 0.7) MRI was performed, per year, throughout the study. Most patients (6,997 patients, 87.0%) had at least one medical device reimbursed during the study (Supplement Tables 2–3).

Discussion

In this first study describing HA-RRMS French adult patients based on the national health insurance database, we identified 9,596 incident patients over 2010–2015 and followed them up for 4 years, on average. Almost $\frac{3}{4}$ of incident patients were women and the mean age at inclusion was about 40 years old. Assuming that patients were diagnosed with MS around the time they obtained full coverage of MS medical expenses, the median time between MS diagnosis and HA-RRMS was about 5 years. Between 2010 and 2015, among adults 20 years old and above covered by the NHI General Scheme, the age-standardized prevalence rate increased from 11.0 to 26.5 HA-RRMS cases per 100,000 and the age-standardized incidence rate ranged from 2.6 to 4.5 new HA-RRMS cases per 100,000. On average, patients experienced 1 relapse every other year. At inclusion, about 70% of patients were taking an HE-DMD, for a mean duration of 3.5 years. Patient management involved many healthcare professionals and exams with, on average, around 8 GP, 1 neurologist, 28 nurse, and 26 physiotherapist visits, 1 MRI and 4 complete blood counts per year.

We observed a marked increase in the annual age-standardized prevalence rate of HA-RRMS over the study period, together with an increase in the age-standardized incidence rate starting in 2012. Rather than an increase in disease prevalence, this surge is most likely explained by the launch of fingolimod (used as inclusion criterion) on the French market in 2011. This likely also explains why more patients switched from natalizumab to fingolimod than the opposite and more patients not treated with an HE-DMD at the index date initiated fingolimod than natalizumab.

A previous study, based on the SNIIRAM database and conducted by Foulon et al.,¹⁶ estimated that about 98,500 persons older than 20 had MS in France in 2012, corresponding to a national crude MS prevalence of 199 per 100,000. We estimated that about 7,300 persons older than 20 had an HA-RRMS in 2012, corresponding to a crude prevalence of 17 per 100,000. Based on these data, HA-RRMS patients would represent around 8% of MS patients. This proportion is slightly lower than that reported by the French Health Authorities around the same period among MS patients followed-up by physicians (11%).¹⁷ The median age at MS diagnosis was 40 years old in the Roux et al. study.² The median age of new HA-RRMS cases was 39 years old in our study (adults only) and the estimated median time to MS diagnosis was about 5 years prior to HA-RRMS. These results could imply that, among patients who experience HA-RRMS, HA-RRMS happens early in the MS disease history and that HA-RRMS patients are diagnosed with MS at a younger age than the overall MS population.

The crude HA-RRMS mortality rate increased over the study period with the highest crude rate of 389 deaths per 100,000 HA-RRMS cases (age 20 and above) in 2015 and an SMR of 2.1 compared to general population. The 2013 crude MS mortality rate was 1,370 deaths per 100,000 MS cases (all ages) with an SMR of 2.6.¹⁶ That year, the HA-RRMS crude mortality rate was 189 deaths per 100,000 HA-RRMS cases (age 20 and above) and the SMR 1.2 (95% CI 0.6–1.7). These results are in favor of a lower mortality among HA-RRMS patients compared to the whole MS patient population. This could be explained by the fact that HA-RRMS are younger than MS patients, or improved disease management when HE-DMD are taken early.

In this study with a mean follow-up of 4.0 years, HE-DMD therapy lasted, on average, for 3.5 years and most but not all patients were treated with an HE-DMD at one point during the study. This highlights the need for additional HE-DMD options, as they should be initiated as early as possible.^{7,11} Patients who have not been observed to have taking HE-DMD could be relying on other treatments (DMD, symptomatic treatments, other immunosuppressants, rituximab and mitoxantrone) or perhaps be refusing HE-DMD due to several reasons (not available in the claims database): suboptimal efficacy, tolerability issues, or concern about potential tolerability issue.⁹ Another possibility is that, despite using multiple criteria and having been validated by experts, our algorithm also detects a small proportion of MS patients who experience at least one relapse, have an MRI, a DMD and a switch of DMD, and yet do not have an HA-RRMS. Nevertheless, the algorithm successfully identified genuine HA-RRMS patients, the therapeutic management of these patients and its evolution with the introduction of fingolimod. Such algorithm is all the more needed than the identification of these patients is still being debated,^{5,6} earlier management improves patient outcomes,⁷ and new drugs are now available.

Finally, our study showed a large spectrum of healthcare professionals involved in the management of HA-RRMS. The high number of hospital care visits and the higher number of visits the first year of follow-up among the patients with at least one visit is partly related to drug dispensing. The high number of relapses in our population is at least partly due to our selection criteria (30% of patients were included for having one or more relapses).

This study has several strengths. The first one is the use of comprehensive data from the French administrative healthcare claims database, specifically from the General Scheme, covering 76% of the French population, offering improved coverage compared to studies based on the MS French observatory¹⁸ and the MS regional registry in Lorraine.¹⁹ The second one is the absence of patient participation bias because the data are routinely collected for reimbursement purposes and not specifically for this study. The third one is the longer follow-up compared to other studies which allows accurate capture of disease management, including treatment changes.

This study also has limitations that must be considered when interpreting the results. In the absence of clinical data (such as MS relapses) in the database which would allow to ascertain HA-RRMS patients, we had to develop an algorithm. This algorithm should be used in additional studies to confirm its capacity to capture all HA-RRMS patients and updated with new HE-DMDs. Our results apply to that

period only, as new treatments have since been released. Using an anonymous database hinders access to additional information on patient and disease characteristics through patient questionnaires (e.g. the Expanded Disability Status Scale used in MS studies). In that respect, linking claims data to MS registry data would further our understanding of the HA-RRMS patient population and their therapeutic management.

This real-world study around the time when HE-DMDs became available offers some valuable insight into the HA-RRMS population. Our estimated proportion of HA-RRMS patient in the whole MS population is similar to that previously reported, thereby bringing consistency to our algorithm. Based on three criteria, our method can contribute to the much needed and still debated definition of HA-RRMS. Despite the need for a long-term care, some patients never took HE-DMDs, highlighting the need for additional treatment options.

Declarations

Ethics approval and consent to participate

The study has been approved by the Committee for research, studies and evaluations in the field of health (Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé, CEREEES). The CEREEES has been replaced by the CESREES in 2020. See process at <https://www.health-data-hub.fr/utilisateur-de-donnees>. Raw data have been made available after acceptance from the French data protection and Ethic authority (Comité National d'informatique et Liberté, CNIL): CNIL: decision DR-2018-099.

Consent for publication

The SNIIRAM contains comprehensive individualized and anonymous data on all healthcare expenditures reimbursed by the French NHI. Thus, no consent for publication was needed.

Availability of data and material

Data from the National Health data system in France (Système National des Données de Santé, SNDS) are publicly available (<https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees>) after acceptance from the French data protection authority (Comité National d'informatique et Liberté, CNIL). The datasets analysed during the current study are available from co-author Ludovic Lamarsalle (llamarsalle@hevaweb.com) on reasonable request. All data generated or analysed during this study are included in this published article.

Competing interests

EP, MP, OC, and BvH are employees of Merck S.A.S., an affiliate of Merck KGaA, Darmstadt, Germany. FR and LL are employees of the CRO HEVA. AK and OV are two independent experts who received fees for participating in the scientific committee of the study.

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Authors' contributions

AK, MP, EM, LL, FR, BvH and OV made the study protocol and analyzed the data; OC analyzed the data and was a major contributor to the writing of the draft manuscript. All authors reviewed and approved the final version of the manuscript.

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Tables

Table 1 Demographic characteristics of incident highly active relapsing-remitting multiple sclerosis adults at index date, 2010–2017

	HA-RRMS incident population
Age (n = 9,596), mean (SD), years	39.9 (10.5)
Female sex (n = 9,596), no. (%)	7,067 (73.7%)
MS LTD status (n = 9,596), no. (%)	9,539 (99.4%)
Time since MS LTD status (n = 9,539), no. (%)	
>10 years prior to index date	2,781 (29.2%)
]5;10] years prior to index date	2,312 (24.2%)
≤5 years prior to index date	4,352 (45.6%)
After index date	94 (1.0%)
Charlson Comorbidity Index (n = 9,596), no. (%)	
0	6,646 (69.3%)
1	1,406 (14.7%)
2	912 (9.5%)
3-13	632 (6.6%)
Disability pension date among patients <60 years old (n=9,238), no. (%)	1,835 (19.1%)
Disability pension level (n = 1,835), no. (%)	
1	580 (31.6%)
2	1,153 (62.8%)
3 (highest level, more disabilities)	102 (5.6%)
First change in disability pension level during the study among patients <60 years old (n=9,238), no. (%)	
Decrease in pension level (improvement in autonomy)	126 (1.4%)
Increase in pension level (worsening of a autonomy)	1,863 (20.2%)
No change	7,249 (78.5%)
HA-RRMS: highly active relapsing-remitting multiple sclerosis; SD: Standard deviation; MS: multiple sclerosis; LTD: long-term disease	

Table 2 Prevalence and incidence of highly active relapsing-remitting multiple sclerosis adults above the age of 20 in the national health insurance General Scheme, 2010–2015

Year	Person-years, age 20 and above ^a	Number of prevalent cases, age 20 and above	Prevalence		Number of incident cases, age 20 and above	Incidence	
			Crude rate, age 20 and above, per 100,000 person-years (95% CI)	Age-standardized rate, age 20 and above, per 100,000 person-years (95% CI) ^b		Crude rate, age 20 and above, per 100,000 person-years (95% CI)	Age-standardized rate, age 20 and above, per 100,000 person-years (95% CI) ^b
2010	37,176,401	4,420	11.9 (11.5-12.2)	11.0 (10.7-11.4)	1,194	3.2 (3.0-3.4)	3.0 (2.8-3.1)
2011	37,486,895	5,433	14.5 (14.1-14.9)	13.5 (13.1-13.8)	1,049	2.8 (2.6-3.0)	2.6 (2.4-2.8)
2012	44,132,973	7,333	16.6 (16.2-17.0)	15.8 (15.5-16.2)	2,083	4.7 (4.5-4.9)	4.5 (4.3-4.7)
2013	44,467,091	8,997	20.2 (19.8-20.7)	19.3 (18.9-19.7)	1,895	4.3 (4.1-4.5)	4.1 (3.9-4.2)
2014	38,758,725	10,209	26.3 (25.8-26.9)	24.7 (24.2-25.2)	1,774	4.6 (4.4-4.8)	4.3 (4.1-4.5)
2015	39,207,109	11,046	28.2 (27.7-28.7)	26.5 (26.0-26.9)	1,490	3.8 (3.6-4.0)	3.6 (3.4-3.8)

^a Number of persons affiliated to the National Health Insurance General Scheme. Source: CNAM (Caisse Nationale d'Assurance Maladie)

^b Rates are standardized for gender and 5-year age group using the population living in France on January 1st, 2016 as the reference population. 111 incident patients were under 20 years old.

CI: confidence interval

Table 3 Mortality among prevalent highly active relapsing-remitting multiple sclerosis adults above the age of 20, 2010–2015

Year	Number of HA-RRMS prevalent cases, age 20 and above	Number of deaths, age 20 and above	Mortality	
			Crude rate, age 20 and above, per 100,000 person-years (95% CI)	Mortality rate ratio ^a , age 20 and above (95% CI)
2010	4,420	5	113 (47-271)	0.8 (0.1-1.5)
2011	5,433	16	294 (180-480)	2.0 (1.0-3.0)
2012	7,333	12	164 (93-288)	1.1 (0.5-1.7)
2013	8,997	17	189 (117-304)	1.2 (0.6-1.7)
2014	10,209	29	284 (197-408)	1.7 (1.1-2.3)
2015	11,046	43	389 (289-524)	2.1 (1.5-2.8)

HA-RRMS: highly active relapsing-remitting multiple sclerosis; CI: confidence interval
^a The mortality of HA-RRMS patients is compared to the mortality in the French population on January 1st, 2016

Table 4 Disease-modifying treatment and symptomatic treatment of incident highly active relapsing-remitting multiple sclerosis adults within the two years prior to index date, 2010-2017

	HA-RRMS incident population
Number of DMD (n = 9,596), no. (%)	
None	2,394 (25.0%)
1	6,379 (66.5%)
2, successively	807 (8.4%)
3-4, successively	16 (0.2%)
Type of DMD ^a (n = 7,202), no. (%)	
1 drug	6,379 (88.6%)
IFN β	4,278 (59.4%)
GA	1,874 (26.0%)
DMF	146 (2.0%)
TRF	81 (1.1%)
2 drugs, successively	807 (11.2%)
IFN β and GA	573 (8.0%)
IFN β and DMF	88 (1.2%)
Other duo	146 (2.0%)
3 or 4 drugs, successively	16 (0.2%)
Treated by methylprednisolone (≥ 1 g) (n = 9,596), no. (%)	2,226 (23.2%)
Treated by symptomatic treatments ^a (n = 9,596), no. (%)	9,148 (95.3%)

^a list of treatments in supplemental Table 1
HA-RRMS: highly active relapsing-remitting multiple sclerosis; DMD: disease-modifying drug; IFN β : Interferon beta; GA: Glatiramer Acetate; DMF: Dimethyl Fumarate; TRF: Teriflunomide

Table 5 Disease-modifying treatment of incident highly active relapsing-remitting multiple sclerosis adults during follow-up, 2010-2017

HA-RRMS incident population	
Number of DMD (n = 9,596), no. (%)	
None	5,787 (60.3%)
1	2,384 (24.8%)
2, successively	1,154 (12.0%)
3-4, successively	271 (2.8%)
Type of DMD ^a (n = 3,809), no. (%)	
1 drug	2,384 (62.6%)
IFN β	860 (22.6%)
GA	522 (13.7%)
DMF	486 (12.8%)
TRF	247 (6.5%)
2 drugs, successively	1,154 (30.3%)
IFN β and DMF	310 (8.1%)
IFN β and GA	187 (4.9%)
IFN β and TRF	162 (4.3%)
DMF and GA	154 (4.0%)
DMF and TRF	129 (3.4%)
Other duo	212 (5.6%)
3 or 4 drugs, successively	27 (7.1%)

^a list of treatments in supplemental Table 1

HA-RRMS: highly active relapsing-remitting multiple sclerosis; DMD: disease-modifying drug; IFN β : Interferon beta; GA: Glatiramer Acetate; DMF: Dimethyl Fumarate; TRF: Teriflunomide

Table 6 Treatment switches incident highly active relapsing-remitting multiple sclerosis adults during follow-up, 2010-2017

	Patients with a switch from Fingolimod among the 5,865 patients ever treated with Fingolimod	Patients with a switch from Natalizumab among the 3,664 patients ever treated with Natalizumab	Patients with a switch from Fingolimod or Natalizumab among the 9,529 patients ever treated by Fingolimod or Natalizumab ^c
Switch to a DMD ^a no. (%)	436 (7.4%)	367 (10.0%)	803 (8.4%)
DMF	177 (3.0%)	138 (3.8%)	315 (3.3%)
GA	101 (1.7%)	102 (2.8%)	203 (2.1%)
IFN β	78 (1.3%)	89 (2.4%)	167 (1.8%)
TRF	96 (1.6%)	50 (1.4%)	146 (1.5%)
Switch to Rituximab ^b	179 (3.1%)	146 (4.0%)	325 (3.4%)
Switch to the other HE DMD (Fingolimod or Natalizumab), no. (%)	260 (4.4%)	1,023 (27.9%)	1,283 (14.5%)

^a Excluding Biotine

^b Rituximab has no indication in multiple sclerosis

^c Some patients are counted twice in this sample, as they were treated with both drugs

DMD: disease-modifying drug; IFN β : Interferon beta; GA: Glatiramer Acetate; DMF: Dimethyl Fumarate; TRF: Teriflunomide; HE DMD: High efficacy disease-modifying drug

Table 7 Multiple sclerosis-related hospitalizations in incident highly active relapsing-remitting multiple sclerosis adults, 2010-2017

	HA-RRMS incident population
At least one hospitalization with a principal diagnosis or related diagnosis of MS, within the two years prior to index date (n = 9,596), no. (%)	4,846 (50.5%)
Number of hospitalizations with a principal diagnosis or related diagnosis of MS among patients with at least one hospitalization, within the two years prior to index date (n = 4,846), mean (SD)	2.8 (3.4)
At least one hospitalization with a principal diagnosis or related diagnosis of MS and at least 2 years of follow-up, during follow-up (n = 8,045), no. (%)	7,485 (93.0%)
Number of hospitalizations among patients with at least one hospitalization during the follow-up and at least 2 years of follow-up, during first year of follow-up (n = 7,485), mean (SD)	6.3 (5.8)
Annual number of hospitalizations among patients with at least one hospitalization during the follow-up and at least 2 years of follow-up, during follow-up (n = 7,485), mean (SD)	4.7 (4.6)

HA-RRMS: highly active relapsing-remitting multiple sclerosis; MS: multiple sclerosis; SD: Standard deviation. The definition of MS-related hospitalization is in Supplement 3.

Table 8 Multiple sclerosis-related outpatient, hospital practitioner, and other medical professional visits in incident highly active relapsing-remitting multiple sclerosis adults with at least 2 years of follow-up (n = 8,045), 2010-2017

	1 st year of follow-up		Whole follow-up	
	No. of visits, mean (SD)	Number of patients with at least 1 visit, no. (%)	Annual no. of visits, mean (SD)	Number of patients with at least 1 visit, no. (%)
General practitioner	8.8 (7.1)	7,920 (98.5%)	8.2 (5.9)	8,004 (99.5%)
Nurse	22.9 (131.5)	4,833 (60.1%)	28.2 (145.2)	6,927 (86.1%)
Dentist	2.3 (4.1)	3,863 (48.0%)	2.2 (2.5)	6,381 (79.3%)
Physiotherapist	24.2 (39.6)	4,104 (51.0%)	26.0 (37.9)	5,906 (73.4%)
Ophthalmologist	1.1 (1.8)	3,507 (43.6%)	0.9 (1.1)	5,827 (72.4%)
Gynecologist (n = 5,946 women)	0.9 (2.3)	2,250 (37.8%)	1.1 (2.0)	3,711 (62.4%)
Neurologist	0.9 (1.8)	2,334 (29.0%)	0.8 (1.4)	3,342 (42.7%)
Dermatologist	0.3 (0.9)	1,386 (17.2%)	0.3 (0.6)	3,420 (42.5%)
Cardiologist	0.2 (0.7)	624 (7.8%)	0.2 (0.4)	1,759 (21.9%)
Orthoptist	0.5 (3.3)	618 (7.7%)	0.3 (1.9)	1,405 (17.5%)
Gastroenterologist	0.1 (0.6)	362 (4.5%)	0.1 (0.3)	1,152 (14.3%)
Psychiatrist	0.8 (6.6)	568 (7.1%)	0.7 (4.7)	1,047 (13.0%)
Podiatrist	0.1 (0.4)	215 (3.1%)	0.1 (0.4)	870 (10.8%)
Hospital practitioner ^a	0.1 (1.3)	220 (2.7%)	0.1 (0.8)	842 (10.5%)
Speech therapist	1.0 (6.8)	314 (3.9%)	1.3 (6.5)	682 (8.5%)
Urologist	0.1 (0.3)	221 (2.8%)	0.1 (0.3)	632 (7.9%)
Medicine and rehabilitation physician	0.1 (1.9)	143 (1.8%)	0.1 (1.9)	422 (5.3%)
Neurosurgeon	0.0 (0.1)	18 (0.2%)	0.0 (0.1)	83 (1.0%)

All secondary care visits accounted for were those held in the community and not at the hospital. All hospital practitioners' visits were combined due to inconsistent reliability of the hospital practitioner specialty in the database. ^a Excludes visits during hospital stays because they are included in the price of the hospital stay.

Figures

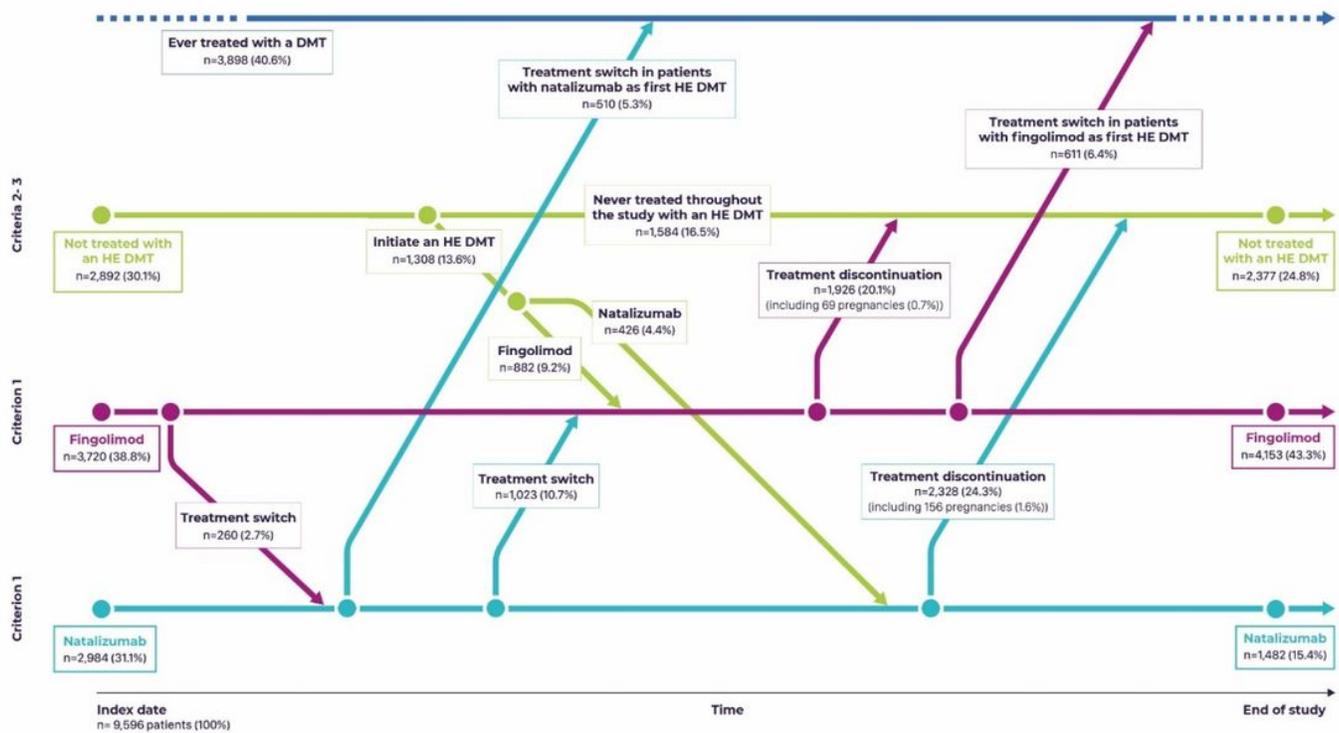


Figure 1

Treatments in incident highly active relapsing-remitting multiple sclerosis adults during the follow-up, over 2010–2017

Supplementary Files

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- [Supplementalmaterial.docx](#)