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ORIGINAL ARTICLE

Disability progression in multiple sclerosis patients using early first-line treatments

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Abstract

Background and purpose: Therapeutic management of relapsing–remitting multiple sclerosis (RRMS) has evolved towards early treatment. The objective was to assess the impact of early treatment initiation on disability progression amongst RRMS first-line-treated patients.

Methods: This study included all incident RRMS cases starting interferon or glatiramer acetate for the first time from 1 January 1996 to 31 December 2012 ($N = 5279$) from 10 MS expert Observatoire Français de la Sclérose en Plaques centres. The delay from treatment start to attaining an irreversible Expanded Disability Status Scale (EDSS) score of 3.0 was compared between the early group ($N = 1882$; treated within 12 months following MS clinical onset) and the later group using propensity score weighted Kaplan–Meier methods, overall and stratified by age.

Results: Overall, the restricted mean time before reaching EDSS 3.0 from treatment start was 11 years and 2 months for patients treated within the year following MS clinical onset and 10 years and 7 months for patients treated later. Thus, early treated patients gained 7 months (95% confidence interval [CI] 4–11 months) in the time to reach EDSS 3.0 compared to patients treated later (treatment start delayed by 28 months). The difference in restricted mean time was respectively 6 months (95% CI 1–10 months) and 14 months (95% CI 4–24 months) in the ≤40 years age group and in the >40 years age group, in favour of the early group.

Conclusions: Early treatment initiation resulted in a significant reduction of disability progression amongst patients with RRMS, and also amongst older patients.

KEYWORDS
beta-interferon, disability progression, early treatment, glatiramer acetate, multiple sclerosis, observational studies, propensity score

The OFSEP investigators are listed in the Appendix A.

INTRODUCTION

In the last 20 years, treatment options for relapsing–remitting multiple sclerosis (RRMS) have improved due to the increased numbers of approved disease-modifying therapies (DMTs). These drugs are administered in many ways including injections, pills or in-hospital infusions and the treatment choices are driven by information concerning the risk–benefit balance and the expanding volume of experience from their use by neurologists in real-life settings [1]. Choosing a DMT is complex, taking into account its efficacy and the severity of the proven and/or potential risks. Some available DMTs, such as first-line injectable therapies, have milder efficacies and better safety profiles, whereas other therapies such as natalizumab, fingolimod, mitoxantrone or alemtuzumab are more effective but are associated with a higher risk profile which may exhibit rare but severe adverse events such as progressive multifocal leukoencephalopathy, infection or leukaemia. Choosing a first-line DMT and its initiation timing is a complex process undertaken according to patient characteristics, particularly age, gender and comorbidity. Additionally, disease severity, drug safety profiles and the accessibility of relevant drugs are taken into account [2].

There is accumulating evidence that suggests that action should be initiated as soon as the diagnosis of MS is made [3]. Natural history and immunopathological studies have shown that what happens early during the inflammation phase of the disease influences the long-term outcome, particularly regarding the development of irreversible neurological disability [3, 4].

Numerous clinical trials (including their extensions) have pointed out that early treatment is beneficial in increasing the time of conversion from a first attack to a clinically definite case of MS compared with delayed treatment [5–10]. Moreover, early therapeutic intervention is also strongly recommended by the European Committee of Treatment and Research in Multiple Sclerosis and the European Academy of Neurology [2].

Regarding the benefits of early intervention on disability progression, available findings show that the initiation of early treatment seems to delay disability progression [11–17]. However, results from real-life studies remain poorly documented [18–20]. In that context, the objective of the present study was to assess the impact of early treatment initiation on disability progression, both overall and stratified by age, amongst RRMS patients treated initially with first-line DMTs.

METHODS

Data collection

Data were obtained routinely from the Observatoire Français de la Sclérose en Plaques (OFSEP), a French network of MS expert centres, using the European Database for Multiple Sclerosis (EDMUS) software to collect prospective standardized data on MS patients [21, 22]. Data from the 10 oldest MS expert centres in France (data collection started before 2001; Lyon, Nancy, Bordeaux, Rennes, Toulouse, Nice, Clermont-Ferrand, Dijon, Besançon and Nîmes) were extracted on 15 December 2018 and produced an initial cohort of 34,582 patients.

Study population

All incident RRMS cases starting an approved first-line injectable treatment (interferon or glatiramer acetate) for the first time from 1 January 1996 to 31 December 2012 were included in our study. A minimum of three visits and a follow-up of 5 years from MS clinical onset were also required for inclusion. Patients starting natalizumab, fingolimod and mitoxantrone as a first treatment were excluded. The study period started in 1996 because it corresponded to the approval of the first DMT (beta-interferon 1b) in France. The period ended in 2012 to get sufficient follow-up after treatment initiation to observe any disability progression. During this period, only beta-interferon and glatiramer acetate were available as first-line DMTs. All patients who had a sustained 6-month confirmed Expanded Disability Status Scale (EDSS) score of 3.0 or more before starting treatment were also excluded.

Treatment exposure

All patients who were exposed for at least 1 day to a first-line DMT (beta-interferon and glatiramer acetate) during the study period were considered as treated. The delay from MS clinical onset to first treatment initiation was used to define groups. Early treatment was defined as an initiation within 12 months from MS clinical onset, whereas later treatment was defined as an initiation after 12 months.

Outcome

Outcome was the time from the start of treatment (baseline) to the attainment of a 6-month confirmed EDSS score of 3.0, sustained until the final visit. EDSS scores were collected outside of relapses.

Variables

The following variables were considered in the analysis: sex, age at MS clinical onset and at treatment start, year of MS clinical onset, number of relapses in the 12 months preceding treatment initiation, EDSS scores (outside of relapses) within 12 months before treatment start and centre. In the case of multiple EDSS entries, the nearest to treatment start was selected. The variable related to EDSS score before treatment start included a 'missing' category.

Statistical analysis

Characteristics were described using the usual indicators. The proportion of patients considered as treated early was calculated for each MS clinical onset year over the study period. The median follow-up durations were computed using the reverse Kaplan–Meier method [23]. Patients treated early were compared to patients treated later. To control indication bias, a propensity score (PS) was used and obtained from a logistic regression including variables associated with the outcome (level of significance at 20%) [24]. All variables were considered eligible and the variables finally included in each PS model are summarized in Table S1. Two PS models were performed, that is, one which included age at MS clinical onset and another that included age at treatment start. The outcome was then studied using Kaplan–Meier methods weighted by a stabilized inverse probability of treatment weights. The weights were stabilized by multiplication by the marginal probability of receiving the treatment [25]. According to both PS models, the restricted mean survival time (RMST) [26], that is, the restricted mean time before reaching the outcome, between the two groups was reported and compared. A difference in the RMST showed the gain or loss of time before reaching an outcome in one group compared to the other. The outcome was also studied using Cox proportional hazard models weighted by the stabilized inverse probability of treatment weights with robust estimation of variance [27]. Confidence intervals were obtained by bootstrap (k = 1000) [28]. Analyses were conducted based on an intention-to-treat framework meaning that the follow-up was not censored in the case of treatment cessation. Lastly, an analysis stratified on age was performed at MS clinical onset with a cut-off set at 40 years. This analysis followed the same statistical plan. As a sensitivity analysis, the analysis was replicated after excluding patients with missing EDSS score within 12 months before treatment start. Analyses were performed using R software (R 4.0.3), and the package RISCA [29] was used to obtain the weighted Kaplan–Meier estimators.

RESULTS

Characteristics of the study population

Overall, 5279 patients fulfilled the inclusion criteria and were included in the study (Figure 1). The first treatment was beta-interferon for 82% of the patients and glatiramer acetate for the remaining 18%. Table 1 provides patient characteristics at treatment start. The median age at MS clinical onset was 31 years (interquartile range [IQR] 25–38). One-third of patients had at least two relapses in the 12 months before treatment start. The baseline EDSS score was 2.0 or more for 42% of patients.

Overall, the median delay from MS clinical onset to treatment start was 1.6 years (IQR = 0.7–3.7) and the median follow-up duration from treatment start was 9.5 years (95% confidence interval [CI] 9.3–9.7). The definition of early led us to consider 1882 patients (36%) as treated early. As shown in Figure 2, the percentage of patients treated early increased over time. After treatment initiation, 923 of the early treated patients (49%) and 1256 (36%) of the later treated patients escalated to higher-efficacy agents (natalizumab, fingolimod, alemtuzumab or mitoxantrone). Over 15 years, the restricted mean times from start of the initial treatment before escalation were respectively 9.6 years (95% CI 9.3–9.9) and 10.6 years (95% CI 10.4–10.8) in the two groups.

Comparison between early and later treated patients on disability progression

The PS distributions showed a noticeable overlap between the two groups, as shown in Figure S1. After weighting, the two groups were well balanced with standardized mean differences or Mahalanobis distances of around 10% for all patients' characteristics (Table S2).

Overall, the restricted mean survival time before reaching an EDSS score of 3.0 was 10 years and 10 months (10 years 7 months

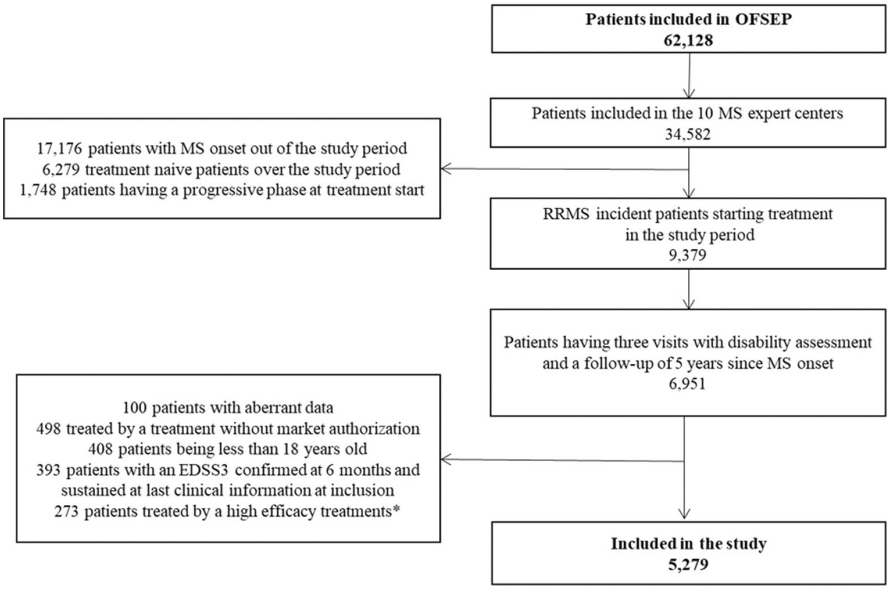

FIGURE 1 Study flowchart to assess the disability progression in multiple sclerosis (MS) patients using early first-line treatment

TABLE 1 Multiple sclerosis (MS) patient characteristics at treatment initiation: overall and according to age at MS clinical onset

	All	Age at MS clinical onset	
		≤40 years old group	>40 years old group
	N = 5279	*N* = 4197	*N* = 1082
Sex (female)[a]	4010 (76%)	3159 (75.3%)	8.51 (78.7%)
Age at MS clinical onset[b]	30.9 (25.2–38.4)	28.4 (24.1–33.5)	44.5 (41.9–48.2)
Age at treatment start[b]	33.9 (27.7–41.2)	31.3 (26.5–36.6)	47.2 (44–51.4)
MS duration at treatment start[b]	1.6 (0.7–3.7)	1.7 (0.7–3.9)	1.5 (0.7–3.3)
Number of relapses within 12 months before treatment start[a]			
0	755 (14.3%)	583 (13.9%)	172 (15.9%)
1	2716 (51.4%)	2135 (50.9%)	581 (53.7%)
2	1410 (26.7%)	1135 (27%)	275 (25.4%)
≥3	398 (7.5%)	344 (8.2%)	54 (5%)
EDSS within 12 months before treatment start[a,c]			
[0.0; 1.5]	1740 (33%)	1438 (34.3%)	302 (27.9%)
[2.0; 3.5]	1161 (22%)	859 (20.5%)	302 (27.9%)
≥4	111 (2.1%)	88 (2.1%)	23 (2.1%)
Missing	2267 (42.9%)	1812 (43.2%)	455 (42.1%)
Year of MS onset[a]			
1996–2000	1620 (30.7%)	1620 (30.7%)	280 (25.9%)
2001–2005	1780 (33.7%)	1780 (33.7%)	359 (33.2%)
2006–2012	1879 (35.6%)	1879 (35.6%)	443 (40.9%)

Abbreviation: EDSS, Expanded Disability Status Scale.

[a]N (%).

[b]Median (quartiles).

[c]One-time and unconfirmed measurement.

to 10 years 11 months) over the 15-year study period. Figure 3 shows the Kaplan–Meier estimates for each PS definition, Table 2 summarizes the RMSTs and Figure 5 presents the hazard ratio. After PS weighting, when considering comparable age at MS clinical onset, the RMST before reaching EDSS 3.0 from treatment start was 11 years and 2 months for patients treated within the year following MS clinical onset and 10 years and 7 months for patients treated later. In the early group, the median delay before treatment start from MS clinical onset was 6 months, whereas it was 35 months for patients treated later. Therefore, compared with patients with a median delayed treatment of 28 months, early treated patients gained 7 months (95% CI 4–11 months) in the time to reach an EDSS score of 3.0. Early treated patients showed a 16% decreased hazard of reaching EDSS 3.0 compared with later treated patients (hazard ratio 0.84; 95% CI 0.76–0.92). When patients had a comparable age at treatment start, early treated patients gained 4 months (95% CI 0.5–8 months) in comparison to patients treated later.

Stratification by age

Multiple sclerosis started in patients before the age of 40 amongst 4197 (79%) patients (≤40 years old group) and after 40 years old for 1082 patients (21%) (>40 years old group). The median delays from MS clinical onset to treatment start were 1.7 years (IQR = 0.7–3.9) and 1.5 years respectively (0.7–3.3) in the two subgroups, whose characteristics are shown in Table 1.

After PS weighting, when patients from the ≤40 years old group had comparable age at MS clinical onset, this study showed that, compared with patients with a median delayed treatment of 30 months, early treated patients gained 6 months (95% CI 1–10 months) before reaching an EDSS of 3.0 (Table 2, Figure 4). Early treated patients showed a 13% decreased hazard of reaching EDSS 3.0 compared with later treated patients (Figure 5). No difference was shown for patients who had a comparable age at treatment start.

In the >40 years old group and using the PS including age at MS clinical onset, this study showed that, compared with patients with a median delayed treatment of 26 months, early treated patients gained 14 months (95% CI 4–24 months) before reaching EDSS 3.0. Early treated patients showed 24% decreased hazard of reaching EDSS 3.0 compared with later treated patients (Figure 5). Including age at treatment start in the PS, early treated patients gained approximately 11 months (95% CI 2–21 months) before reaching an EDSS score of 3.0 compared to patients treated later.

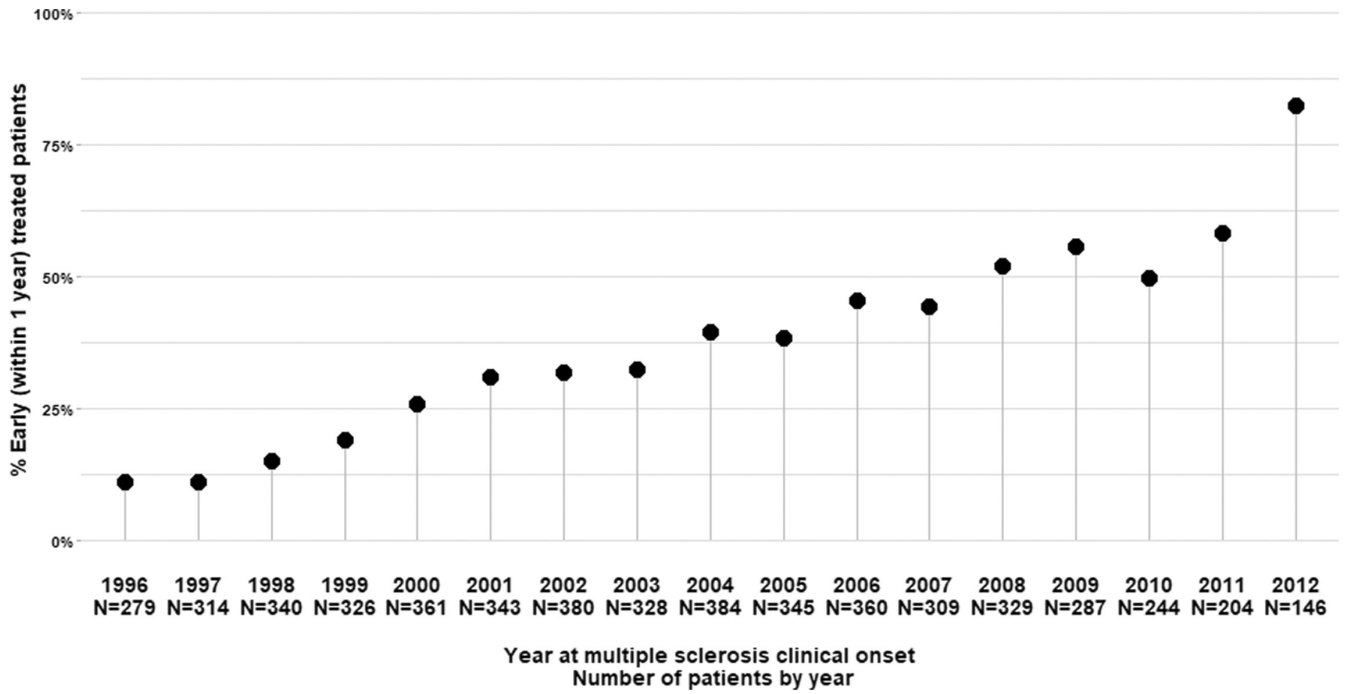

FIGURE 2 Percentage of multiple sclerosis (MS) patients treated early (defined as an initiation within the year following MS clinical onset) according to year of MS clinical onset

Sensitivity analysis

Results from sensitivity analysis, that is, excluding patients without an EDSS score before treatment start, were close to the main results but somewhat deflated. They also failed to achieve statistical significance, probably due to a lack of power related to the smaller population size (Table 2 and Figure 5).

DISCUSSION

This study aimed to assess the impact of early treatment initiation on disability progression, and a beneficial effect was found. Indeed, by accelerating the median initiation of treatment by 2 years and 4 months, the time to reach 6-month confirmed and sustained EDSS 3.0 was delayed by about 7 months. This significant impact was observed overall and after stratification by age at MS clinical onset (≤40 years old, 6 months for 2 and half years of treatment delayed; >40 years old, 14 months for 2 years of treatment delayed).

The risk of faster disability progression with increased age at MS clinical onset has been shown in large cohort studies [4] which reinforces the need for early control of disease activity overall as well as with older RRMS patients.

In addition, it should be noted that early active MS patients who are more at risk of sequelae after relapse are expected to be seen rapidly by a neurologist and then treated early. Contrarily, MS patients with mild symptoms at first relapse might not be seen by a neurologist and therefore have decreased chances of being treated early. In such patients, treatment initiation may occur several years later. Such differences in MS management may minimize the magnitude of early intervention. Beyond clinical parameters (such as symptom severity and magnetic resonance imaging [MRI] data), an initial consultation with a neurologist is the starting point for treatment initiation. Unfortunately, it was not possible to study the delay between the first consultation with a neurologist and treatment start since the date of a first consultation was not systematically recorded in the OFSEP database.

This study included patients with at least 5 years of follow-up in an MS expert centre, either exclusively or in collaboration with a private neurologist either from disease onset or later in the course of the disease. Although follow-up can be supervised by both MS experts or private neurologists, it is thought that our study probably focused on patients with particular characteristics that required clinical follow-up in MS expert centres. A previous study in Lorraine, France, which compared the natural history of an MS expert centre population with patients followed outside an MS centre, showed that patients in MS expert centres were younger and had earlier disability accumulation [30]. However, the comparison of the overall OFSEP cohort to the MS Lorraine population-based registry (ReLSEP) did not highlight any differences. It cannot be excluded that a potential recruitment bias may have minimized the benefit of early intervention.

In our study, the focus was on only one definition of early treatment initiation. Two other definitions have been considered (within 6 months and within 24 months). The definition studied in this work was chosen as a compromise between concepts and practical considerations. Our study aimed to measure the effect of such therapeutic

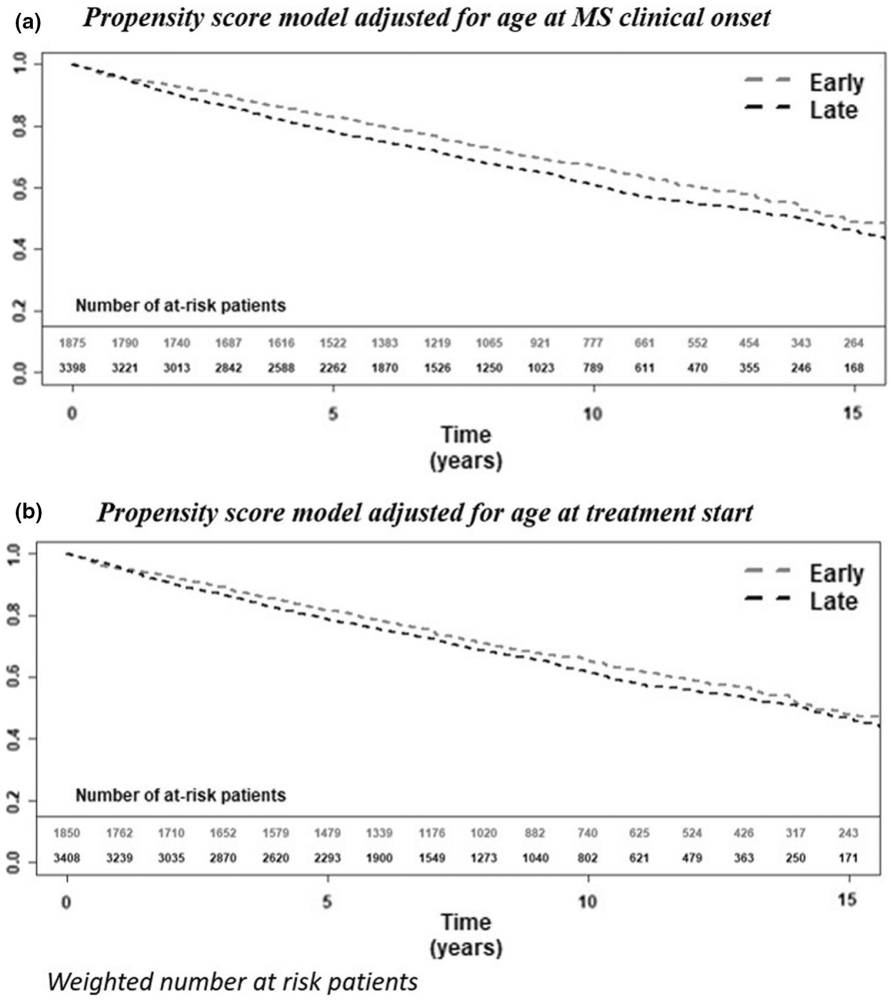

FIGURE 3 Kaplan–Meier estimates of the time before reaching an EDSS score of 3.0 from treatment start for multiple sclerosis (MS) patients treated by a first-line treatment as an initial treatment within the year following MS clinical onset (early) or later (late), according to two propensity score models

TABLE 2 Restricted mean time (RMST) before reaching EDSS 3.0 in early and late treated groups of multiple sclerosis (MS) patients: overall, according to age at MS clinical onset, and in the sensitivity analysis from two propensity score (PS) models

	Early		Late			
Group of patients	Delay before treatment start	RMST	Delay before treatment start	RMST	Median delay in treatment start (months)	Difference in RMST (months)
PS model adjusted for age at MS clinical onset						
All	6 m (4–9 m)	**11 y and 2 m**	35 m (20–61 m)	**10 y and 7 m**	28	**7 [4; 11]**
≤40 years old group	6 m (4–9 m)	**11 y and 6 m**	36 m (21–62 m)	**11 y**	30	**6 [1; 10]**
>40 years old group	6 m (4–9 m)	**9 y and 11 m**	32 m (19–58 m)	**8 y and 8 m**	26	**14 [4; 24]**
Sensitivity analysis[a]	7 m (5–9 m)	**11 y and 7 m**	35 m (20–62 m)	**11 y and 1 m**	28	**6 [0.4; 12]**
PS model adjusted for age at treatment start						
All	6 m (4–9 m)	**11 y**	35 m (20–61 m)	**10 y and 8 m**	28	**4 [0.5; 8]**
≤40 years old group	6 m (4–9 m)	11 y and 5 m	36 m (21–62 m)	11 y and 1 m	30	4 [−0,3; 9]
>40 years old group	6 m (4–9 m)	**9 y and 8 m**	32 m (19–58 m)	**8 y and 9 m**	26	**11 [2; 21]**
Sensitivity analysis[a]	7 m (5–9 m)	**11 y and 6 m**		**11 y and 2 m**	28	**3 [−2; 9]**

Notes: Delay before treatment start: median (quartiles). RMST, restricted mean survival time, corresponds to the restricted mean time before reaching the outcome. For instance, over 15 years restricted, the mean time for patients treated within the year following MS onset to reach an EDSS score of 3 confirmed at 6 months and sustained was 11 years and 2 months, and it was 10 years and 7 months for patients treated later; thus patients treated early reached the outcome around 7 months later than patients treated after 1 year following MS onset. Early treated patients gained 7 months on the time before moderate disability in comparison to patients treated later.

Abbreviations: m, month; MS, multiple sclerosis; PS, propensity score; y; year.

[a]Sensitivity analysis, excluding patients without EDSS 12 months before treatment start.

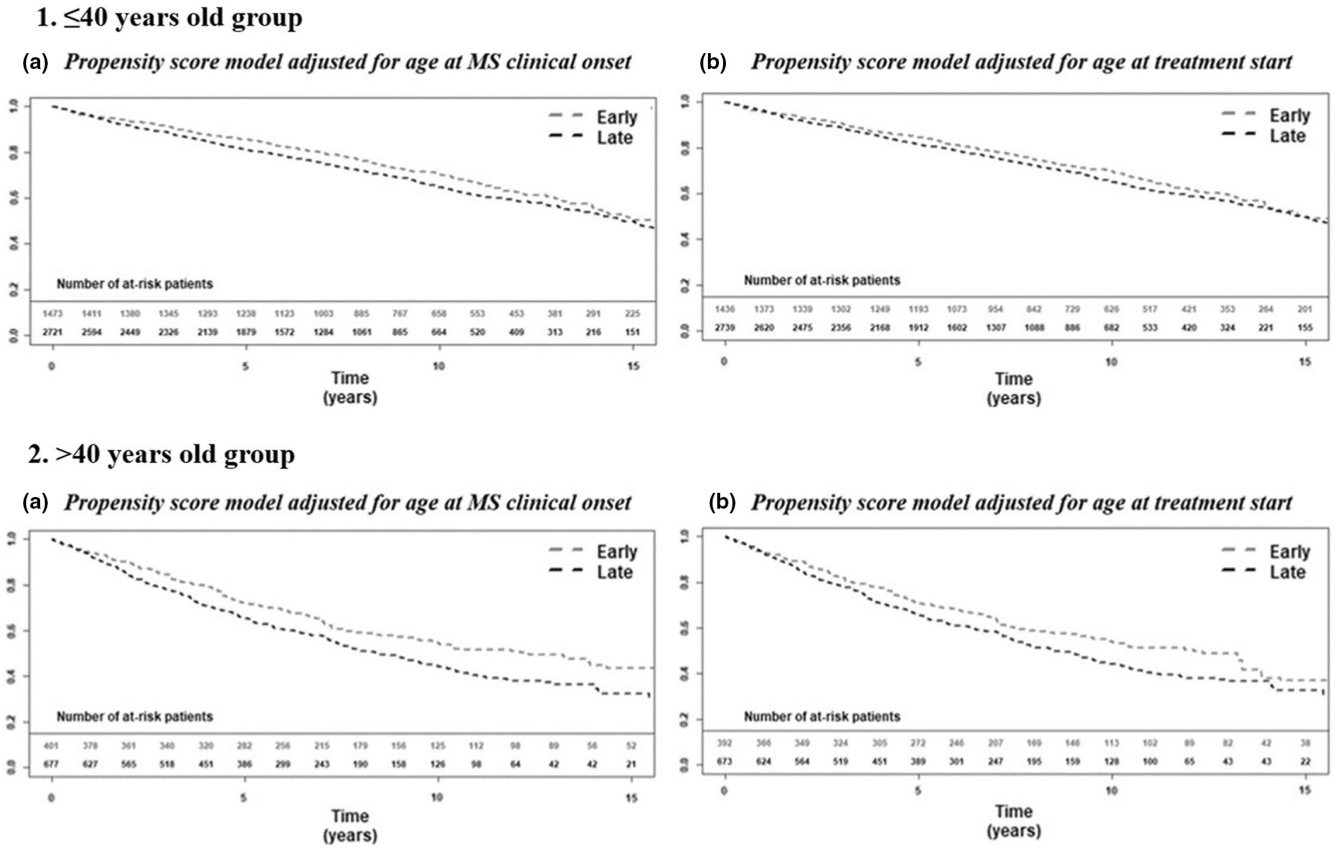

FIGURE 4 Kaplan–Meier estimates of the time before reaching an EDSS score of 3.0 from treatment start for multiple sclerosis (MS) patients treated by a first-line treatment as initial treatment within the year following MS clinical onset (early) or later (late), according to propensity score models and stratified by age at MS clinical onset

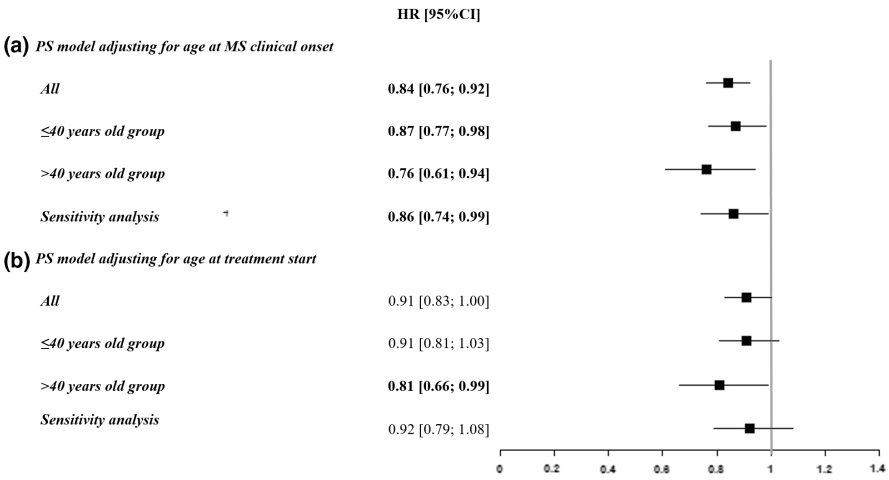

FIGURE 5 Estimated hazard ratio (HR) of early treatment initiation effect on attainment of EDSS 3.0 in multiple sclerosis (MS) patients: overall, according to age at MS clinical onset, and in the sensitivity analysis from two propensity score (PS) models

decision. Treatment changes over follow-up were not considered to avoid adjustment on post-baseline variables.

When comparing this study with the literature, our findings seem less favourable but our result should be interpreted with regard to the delay of treatment. Indeed, in an Italian study focusing on early beta-interferon initiation, a 40% reduction in the risk of reaching EDSS 4.0 was shown for a median delayed treatment of around 5 years [16]. Another recent study performed in Sweden showed that patients who started treatment 3 years after MS onset reached EDSS 4 sooner (hazard ratio 2.64, 95% CI 1.71–4.08) than patients who started treatment within a year from MS onset [14]. Given that these authors confirmed late older age at MS clinical onset as a bad prognostic factor, our group performed a stratified analysis by age at MS clinical onset. A Danish study showed a 42% higher hazard ratio for reaching an EDSS score of 6 compared with early treatment (median treatment delay of 4 years) but did not find consistent results according to age. Indeed, the benefit was significant amongst patients treated before 40 years

of age whereas the result was not significant after 40 years old [17]. Several differences could explain this discrepancy between studies such as data sources (MS expert centres vs. a population-based registry) and outcome (EDSS score of 3 vs. EDSS score of 6). Similar to the study from Chalmer et al. [17], our study included patients over a long time frame, from 1996 to 2013, during which treatment practices have evolved. To limit a potential issue, the year of MS onset was considered in our analyses and was included in the PS models.

One of our expected findings was the evidence of an earlier initiation of DMTs over time which is probably related to several factors or changes related to MS management. First, changes in MS diagnostic criteria enabled earlier MS diagnosis defined as the first clinical demyelinating event [31]. Secondly, treatment indications changed over time allowing treatment from the first relapse instead of waiting for the occurrence of two or three clinical events [5-10]. Finally, the increasing knowledge regarding MS prognosis [1,3,4] combined with a broader experience using DMTs [2] led neurologists to initiate treatment early amongst patients with MS.

With regard to the statistical analysis, two different PS models were chosen to consider two different kinds of information related to patient age. The model adjusted for age at MS clinical onset makes patients comparable in age at the first clinical symptoms which is an important prognostic factor of disability progression. Secondly, the model adjusted for age at treatment start allowed patients to be comparable in age at the time of the treatment decision and therefore combined both age at MS onset and disease duration before treatment start. The difference between the two models is moderate in the group treated early, which is not surprising as there was a maximum of 1 year between the two measurements. The two analyses are presented because they complement each other. Age at treatment start had to be considered since it reflected the age of the treatment decision. However, the analysis based on the age at MS onset reinforced the idea that age is a predominant prognostic factor. Indeed, the beneficial effect of early treatment may be stronger when patients were compared by age at MS clinical onset which was 7 months compared to 4 months gained. Regarding PS model specification, the choice of variables to be included is often discussed in the literature. A statistical criterion was chosen [24,32-34]. Based on that, the number of relapses before treatment start was not included in the PS models. In our opinion, there is no doubt that this parameter is associated with treatment start, but it was not shown to be associated with disability progression in our dataset.

The main limitations of the present study were a lack of MRI data as well as missing data related to the EDSS score at treatment start. During the study period, access to MRI was limited, and this is the reason why relapse events and disability scores were most often used to make therapeutic decisions. Moreover, cerebral and spinal sequences have changed over time and this lack of standardization may limit the use of such data in observational studies.

The second limitation led us to create a 'missing EDSS' category to minimize a potential selection bias coming from EDSS availability. When comparing patients according to baseline EDSS availability, patients with missing baseline EDSS had fewer relapses in the previous year and a longer disease duration (Table S3). As a sensitivity analysis, when excluding patients with missing EDSS, results were close to the main results but not statistically significant.

Outcome was defined from the EDSS scores measured during visits to the MS expert centres. This study did not require any specific rhythm in follow-up consultations besides the request of three visits as inclusion criteria. Visit frequency differed from one MS patient to another; therefore, the risk of inaccurate outcomes due to irregular visits cannot be excluded. In addition, as with all long-term observational studies, it cannot be ruled out that time is running out to observe the EDSS 6.0 outcome, and so this disability hallmark was not considered in this observational study.

In conclusion, the findings of the present study indicate that early treatment initiation (within 12 months following MS clinical onset) becomes more frequent over time in France and results in a significant delayed disability progression amongst patients with relapsing MS. This benefit was found overall and occurs even amongst patients over the age of 40 years. It is considered that our study is in line with the concept of 'time is brain' in MS since such results encourage promoting an early diagnosis of MS and an early treatment. Further research should be considered to compare two strategies: the effect of an early escalation strategy (using both clinical and MRI criteria for DMT monitoring) versus systematic early 'high efficacy' treatment.

AUTHOR CONTRIBUTIONS

Mathilde LEFORT: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); software (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Sandra Vukusic:** Methodology (equal); writing – review and editing (equal). **Romain Casey:** Data curation (equal); methodology (equal); writing – review and editing (equal). **Gilles Edan:** Conceptualization (equal); methodology (equal); project administration (equal); writing – review and editing (equal). **Emmanuelle Leray:** Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

M. Lefort reports that she had travel grants from Roche SAS. S. Vukusic reports that she had consulting and lecturing fees, travel grants and unconditional research support from Biogen, Celgène, Geneuro, Genzyme, MedDay, Merck Serono, Novartis, Roche, Sanofi Aventis and Teva Pharma. R. Casey reports that he had no conflict of interest. G. Edan reports that he had personal honoraria for lectures or consulting from Bayer, Biogen, LFB, Merck, Novartis, Roche, Sanofi; research support from Bayer, Biogen, Genzyme, Merck, Novartis, Roche and Teva Pharma. E. Leray reports that she had consulting and lecture fees or travel grants from Biogen, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Sanofi Aventis and Roche.

DATA AVAILABILITY STATEMENT

The individual data from this study can be obtained upon request and after validation from the OFSEP scientific committee (see: http://www.ofsep.org/fr/)

PATIENT CONSENT

All patients enrolled in the OFSEP database provided informed consent for participation and that their data be stored and used for research. Data confidentiality and safety were ensured according to the recommendations of the French organization Commission Nationale Informatique et Libertés (CNIL). OFSEP received approval for storing clinical, biological and imaging data for research purposes. The study did not require any additional procedures in accordance with French legislation. OFSEP was registered at clinicaltrials.gov under NCT02889965.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX A

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