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► To cite this version:

Xavier Ayrignac, Kevin Bigaut, Jean Pelletier, Jérôme de Seze, Sarah Demortiere, et al.. First line treatment failure: Predictive factors in a cohort of 863 Relapsing Remitting MS patients. *Multiple Sclerosis and Related Disorders*, 2021, 48, pp.102686. 10.1016/j.msard.2020.102686 . hal-03659632

HAL Id: hal-03659632

<https://hal.science/hal-03659632v1>

Submitted on 29 Nov 2024

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First line treatment failure: predictive factors in a cohort of 786 Relapsing Remitting MS patients

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KEYWORDS: Multiple sclerosis, Disease modifying therapies, Treatment failure, Treatment switch, Prognosis

Running title: First line treatment failure in multiple sclerosis

Number of characters in the title: 99

Number of characters in the running title: 50

Number of words in the abstract: 243

Number of words in the body of the manuscript: 2373

Number of figures and tables: 4

Disclosures:

Dr Ayrignac has received consulting and lecturing fees, travel grants, and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, and Teva Pharma.

Dr Bigaut has received travel grants from Biogen and Genzyme.

Dr Pelletier has received consulting and lecturing fees, travel grants, and unconditional research support from Biogen, Genzyme, Novartis, MedDay, Merck Serono, Roche, Sanofi Aventis, and Teva Pharma.

Dr De Sèze has received grants, personal fees, and nonfinancial support from Biogen outside the submitted work, as well as consulting and lecturing fees, travel grants, and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, Sanofi-Aventis, and Teva Pharma

Dr Demortière reports no disclosures relevant to this manuscript

Dr Collongues has received honoraria for consulting or presentation from Biogen Idec, Almirall, Novartis, Merck Serono, LFB, Teva Pharma, Sanofi-Genzyme, and Roche

Dr Maarouf reports no disclosures relevant to this manuscript

F Pinna reports no disclosures relevant to this manuscript

S Aouinti reports no disclosures relevant to this manuscript

Dr Carra-Dallière has received consulting and lecturing fees, and travel grants from Biogen, Genzyme, Novartis, Merck Serono, Roche, and Teva Pharma.

Dr Kremer reports no disclosures relevant to this manuscript

Dr Charif has received consulting and lecturing fees, and travel grants from Biogen, Genzyme, Novartis, Merck Serono, and Teva Pharma.

Dr Picot no disclosures relevant to this manuscript

Dr Labauge has received consulting and lecturing fees, travel grants, and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, and Teva Pharma.

Study funding

This work has been carried out as part of the Observatoire Français de la Sclérose en plaques (OFSEP). OFSEP is supported by a grant provided by the French State and handled by the "Agence Nationale de la Recherche," within the framework of the "Investments for the Future" programme, under the reference ANR-10-COHO-002 Observatoire Français de la Sclérose en plaques (OFSEP).

OFSEP is supported by a grant from the French Government and the Eugène Devic EDMUS Foundation against Multiple Sclerosis. It also received continuous support from the Aide à la Recherche sur la Sclérose en Plaques (ARSEP) Foundation.

Authors' contribution

XA, SA and MCP had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the analysis. XA, JP, JDS and PL helped in concept and design. XA, KB, JP, JDS, SD, NC, AM, CCD, LK, MC and PL performed the acquisition of the data. XA and PL participated in drafting the manuscript. All the authors participated in the critical revision of the manuscript. SA and MCP performed the statistical analysis.

Abstract:

Background: The advent of new, potent, disease-modifying therapies has dramatically changed the management of multiple sclerosis (MS). Along with these possibilities, it is crucial to better recognize patients who are at risk of first line treatment (FLT) failure and switch to highly effective therapies (HET).

Objectives: To identify baseline prognostic factors associated with FLT failure in relapsing remitting MS (RR-MS) patients.

Methods: We included recently diagnosed RR-MS patients starting a FLT identified from 3 French MS centers databases. Baseline characteristics were included in a multivariate Cox analysis to identify the main factors associated with FLT failure.

Results: Seven hundred eighty-six patients were included. We observed an overall rate of treatment failure of 23.5%. The main baseline characteristics associated with treatment failure were age <26 years at treatment start (HR= 2.2, $p<0.001$), EDSS ≥ 2 (HR=2.1, $p<0.001$) and ≥ 2 relapses in the previous year (HR=1.5, $p=0.05$). The association with the presence of gadolinium enhancement on MRI was not statistically significant. EDSS progression was only significantly associated with age at treatment start and treatment failure.

Conclusion: Our series demonstrates that some clinical and imaging factors are associated with treatment failure, and should be considered when planning treatment strategy in patients with recently diagnosed RR-MS.

Introduction

Multiple sclerosis (MS) is a chronic, potentially debilitating, inflammatory disease of the central nervous system. [1],[2] In most of the cases, a relapsing-remitting (RR) phase with clinical relapses and complete or almost complete recovery is followed by a progressive phase with gradual accumulation of disability. [3],[4] In recent years, the therapeutic landscape of MS has dramatically changed, and an increasing number of first line and second line (or highly effective) therapies are currently available to treat relapsing remitting (RR) MS. [5]

Despite their already proven ability to decrease short-term annual relapse rate and disability, first-line therapies (FLT), either injectable or oral forms, have been shown to have less efficacy than second-line treatments also designated as highly effective therapies (HET) on clinical and radiological measures of disease severity.[5]–[8] Moreover, real life studies have shown that early use of HET was associated with lower annualized relapse rate and lower long-term disability progression.[9],[10] Finally, it has been shown that almost 50% of the patients starting FLT will need to switch, mainly for efficacy issues, to HET in the short-term period.[11]–[15]

Regardless of this relatively modest efficacy, FLT have been suggested to improve long-term prognosis of the disease and some patients remain controlled after years suggesting that they are adequate to a significant (possibly small) proportion of patients.[16] The main factors associated with treatment failure and short-term disease activity/progression include age, EDSS, brain and spinal cord lesions, disease duration at treatment initiation as well as evidence of ongoing clinical and/or radiological activity. [11],[17]–[20] Unfortunately, clear predictors of FLT failure, based on baseline clinical, radiological and biological characteristics, are missing. Thus, it is of importance to better identify factors that will predict inefficacy of FLT and require a switch to HET.

The objectives of our study were 1) to assess, over a long-term follow-up, the proportion of patients with FLT failure who will need a switch from a FLT to a HET and 2) to ascertain baseline characteristics predictive of treatment failure and switch to HET which could help to identify patients who will potentially benefit from immediate HET.

Material and methods

Patients and data collection

We performed a multicentre retrospective study involving 3 large tertiary French MS centres (Marseille, Montpellier, Strasbourg) who are part of the OFSEP registry. All French neurologists using European database for multiple sclerosis (EDMUS) agreed to participate and to open the collection of data.[21] Data collection, using a minimal mandatory data set, is organised during routine follow-up outpatients' visits. It includes socioeconomic and demographic variables as well as clinical and magnetic resonance imaging (MRI) follow-up data collected prospectively since the first visit.

Inclusion and exclusion criteria

All patients with a diagnosis of RR-MS or CIS (according to 2010 revision of McDonald criteria) at initiation who had started a FLT in our centres between January 2008 and December 2018 were included.[22]

Patients with insufficient follow-up data, patients who had been previously treated with second-line therapy and patients with delay between disease onset and treatment start > 5 years were excluded.

Data collection

The following data were collected at baseline (treatment initiation): demographics (age, gender), clinical data (date of onset of the disease, disease duration, number of relapses in the previous year, Expanded Disability Status Scale (EDSS), previous relapse type (optic neuritis vs other symptoms), biological results (presence of CSF-specific oligoclonal bands) and brain and spinal-cord MRI (number and location of T2 lesions: ≥ 9 lesions, presence of gadolinium-enhancing lesions, spinal cord involvement). Relapse definition was done according to experienced neurologist-opinion. During patients' follow-up, relapses, EDSS, treatments and MRI results were prospectively collected, usually at least once per year. For the EDSS analysis, an EDSS increase was identified as 1.5-point change if baseline EDSS was 0, a 1-point change if baseline EDSS was ≥ 1 and < 5 and 0.5-point-change if baseline EDSS was > 5 .

Disease-modifying therapies

Considering the therapy, the following variables were collected: date of treatment onset, date of switch to a HET, reason for the switch (either efficacy or intolerance/other reason, extracted from the database). Only switch from FLT to HET for efficacy issue (and not for other reasons such as intolerance or convenience) was considered as a treatment failure. According to previously published randomized controlled trials, teriflunomide, dimethyl fumarate, glatiramer acetate and beta interferons were considered as FLT. They were all classified as a single group. HET considered in the study were: Natalizumab, Fingolimod, Rituximab and Ocrelizumab.

Statistical analysis

Baseline characteristics of the participants were described with frequency and proportions for categorical variables and for continuous ones, with mean and standard deviation if distribution was normal (Shapiro-Wilk statistics), the median and interquartiles (25-75%) were given; if otherwise.

Probability of switch and EDSS increase were estimated by the Kaplan-Meier method. The log rank test was performed to compare the probability of switch and EDSS increase according to the main baseline characteristics. The multivariate analysis was performed with Cox's proportional hazards regression model. All the variables for which the log-rank test returned a p-value ≤ 0.20 were entered in the model. A backward selection of variables was applied. The adjusted hazard ratios and their 95% confidence interval (CI) were reported.

A sensitivity analysis was performed to assess the centre effect in a frailty cox model with a shared gamma frailty included to account for possible within-patient correlation due to the center.

When the risk was not log-linear, continuous variables were transformed as dichotomic variables. The threshold used were determined using ROC with Youden index. The cut-off values were the following: age < 26 years, EDSS < 2 , number of relapses in the previous year < 2 .

All analyses were two-tailed, with a p-value of < 0.05 considered statistically significant. The statistical analyses were carried out using SAS statistical software version 9.1 (Cary, NC, USA) and graphs were

generated using R statistical software (www.r-project.org, version 4.0.2) with ggplot2 package (version 3.3.1).

Ethical considerations

All patients included in the OFSEP cohort sign an informed consent to have their medical data collected in routine practice used after anonymization and aggregation for research purposes. Data confidentiality and safety are ensured according to the recommendations of the French Commission Nationale Informatique et Libertés (CNIL). OFSEP has received approval for storing clinical, biological, and imaging data for research purpose. Patients give informed consent for their data to be stored in the database and used for research, in France and abroad (www.ofsep.org/en/cohort/ofsep-consent). The cohort has been registered to clinicaltrials.gov under the number NCT02889965. According to French law, this study was covered by this general approval and did not require any additional procedure.

Results

Baseline characteristics

Seven hundred eighty-six patients (72% of women) fulfilled the inclusion criteria and were included in the analysis. Baseline characteristics of the participants are depicted in Table 1. Brain and spinal cord MRI were respectively available for 75% and 64% of the patients. The proportion of patients with ≥ 9 T2/FLAIR lesions, gadolinium enhancing lesions and spinal cord lesions were respectively 78.1%, 62.3% and 74.8%. Five hundred twenty-eight patients (67%) had a lumbar puncture performed: CSF-specific oligoclonal bands were identified in 93.2%. FLT choices were respectively Teriflunomide (16.9%), Dimethyl fumarate (15.4%), Glatiramer acetate (24.4%) and interferon beta (43.3%).

Treatment failure

Mean follow-up duration was 5.3 years (± 3.2). Treatment failure was identified in 23.5% of the patients. Mean delay from onset of FLT to treatment switch was 6.7 years (SD: 3.0). The probability of switch were respectively 14.9% at 2 years, 29.9% at 5 years and 42% at 10 years.

The main baseline characteristics associated with treatment failure are disclosed in table 2. Univariate cox analysis showed that the main factors were age < 26 years at FLT start, EDSS ≥ 2 , number of relapses ≥ 2 in previous year, presence of spinal cord lesions and, to a lesser extent gadolinium enhancement (figure 1). A multivariate cox regression (with and without multiple imputations) performed on five hundred thirty patients confirmed that age at treatment start, baseline EDSS and 1-year annualized relapse rate before treatment initiation were the main predictors of a treatment failure (table 2). Even if the presence of gadolinium enhancing lesions was also associated with therapeutic switch, owing to its strong relationship with the age of patients, the association did not remain when age was added as a covariate. Indeed, age of patients with gadolinium enhancement was significantly lower (32.6 +/- 10 years vs 35.4 +/-10.1 years). The sensitivity analysis including the centre effect in a frailty cox model confirmed these results.

According to these results, we assessed the overall probability of switch to HET according to a combination of risk factors. Factors used for this estimation were age (< or ≥ 26 years), baseline EDSS (< or ≥ 2), relapses in the previous year (< or ≥ 2) and the presence of gadolinium enhancing lesions on initial MRI. Taking patients with 0-2 risk factors as a reference, the hazard ratio for patients with 3-4 risk factors was 1.65 (Figure 2, p=0.006). At 2 years, the relative risks of switch were respectively 15% and 25%. At 5 years, these risks were 32.5% and 47%.

EDSS changes

A subgroup of 464 patients with EDSS available at baseline and during the follow-up was analysed. According to our definition, 12.3% of the patients exhibited confirmed EDSS worsening during their follow-up. They were respectively 6.4% at 2 years, 16.3% at 5 years and 36% at 9 years. A multivariate cox regression identified that the only factors associated with EDSS increase were age, treatment failure (respectively HR of 1.05 for each year increase in age and 4.72; both p<0.001) and, albeit not significantly, the identification of spinal cord lesions (p=0.09).

Discussion

Our results confirm that treatment failure requiring switch from FLT to HET is common in patients with recently diagnosed MS with a probability of more than 30% to experience treatment failure and therapeutic switch after a mean follow-up of 5 years.

To date, the main factors known associated with therapeutic failure and short-term disease activity/progression, included: oligoclonal bands, younger age, higher EDSS, brain and spinal cord lesions, disease duration at treatment initiation as well as evidence of ongoing clinical and/or radiological activity within the first year after treatment onset. [11],[18]–[20],[23] Our study, focusing on baseline characteristics at treatment initiation identified that younger age, higher EDSS and 1-year annualized relapse rate were predictors of treatment failure. This is in line with the data from Rio and colleagues and with a recent study by Saccà and colleagues addressing this issue since they also identified younger age and higher EDSS as predictive factors.[11] With respect to OCBs, owing to a high positivity rate (93%), our study was underpowered to identify OCBs as a predictive factor.

In our study, age at treatment onset was strongly associated with treatment failure and switch to HET with an aHR of +/- 2.2 for patients <26 years old. Although this finding can be surprising, one should note that this confirms previously published data specifically addressing treatment failure in distinct cohorts with a mean difference of 4 years between switchers and non-switchers (Sacca, Rio EJM 12, TETER Gauthier). Moreover, in line with previous studies, our results confirm that higher annualized relapse rate and baseline EDSS are predictive of treatment failure (SACCA RIO TETER MAIS AUSSI Gauthier 2009 J Neurol Sc, tintore)

During the last 2 decades, on-treatment MRI has been demonstrated to be an essential tool (with similar odds ratio than relapses alone) to assess disease activity and monitor its evolution.[18],[19] Besides baseline clinical characteristics, our multivariate analysis also suggested that pre-treatment gadolinium enhancing lesions were associated with treatment switch. Nevertheless, this association was not confirmed when age was added as a covariate. This may be, at least partly, explained by the, already reported, correlation between gadolinium enhancement and younger age that we observed.[24]

In contradiction with the recent study by Saccà and colleagues, lesion load and spinal cord lesions were not predictive of treatment switch.[11] This seems not surprising since it has been repeatedly shown that brain and spinal cord lesions are more tightly associated with medium- and long-term disability than with short-term disease activity (and thus, probability of treatment switch to HET). [25]–[28]

Neurologists are in search for predictive markers that should help them to manage patients and predict future evolution of the disease. As it was previously shown by Saccà and colleagues, using a simple score, we were able to identify patients who are at higher risk of treatment failure and thus should be proposed immediate HET as a -FLT. Our results confirm that age (26 years old in our series, 35 years old in the series from Saccà) and EDSS ($<$ or ≥ 2) are essential predictors of treatment failure. Patients who exhibit 3 or 4 of these factors have a nearly 50% increase of the relative risk of treatment switch for therapeutic failure at 2 and 5 years. Nevertheless, we also suggest that none of these factors (even the combination of these factors) can clearly identify patients who are at very high risk of disease breakthrough under FLT and who need treatment escalation to HET.

Besides the risk of ongoing disease activity, it is of importance to identify whether our treatment strategy is associated with a reduction of disability progression. Indeed, in a recent analysis by Malpas and colleagues, it has been demonstrated that age > 35 years old at MS onset, EDSS ≥ 3 in the first year and having pyramidal signs in the first year were predictive of reaching EDSS ≥ 6 within 10 years.[29] Although our analysis was limited by the relatively small size of our cohort, we could confirm that age at MS onset was associated with EDSS worsening. Moreover, it has frequently been shown that delaying treatment initiation and treatment switch could be associated with worse clinical outcomes. [9],[10],[30] In our study, median delay to treatment switch was only 24 months suggesting that, at the beginning of the disease, patients are closely monitored and most of the patients rapidly switch in the presence of clinical and/or radiological evidence of disease activity. Nevertheless, despite a relatively rapid change from FLT to HET, patients switching to HET had a 5 times higher risk of EDSS increase than in patients remaining on FLT.

Our study has some limitations mainly related to its retrospective and observational design as well as its relatively small sample size. They notably include the potential heterogeneity of the data from 3 different centres (indication bias, treatments and attitude toward treatments) but taking the center effect into account in a frailty cox model did not modify the results obtained in terms of estimation. Moreover, owing to the more recent availability of ocrelizumab, we may suppose that, mainly due to its convenience, switch if currently more rapidly considered leading to historical bias. Nevertheless, our data did not evidence significant changes between epochs (data not shown).

In conclusion, we confirm that, in a relatively contemporary cohort, more than 30% of the patients who initiate FLT will switch to second line therapies within less than 5 years of treatment. Although these data need further validation in independent and larger cohorts, we propose that younger patients with EDSS \geq 2 and high annualized relapse rate as well as gadolinium enhancing lesions, should benefit from HET as a FLT.

References

1. **Reich DS, Lucchinetti CF, Calabresi PA.** Multiple Sclerosis. *N. Engl. J. Med.* 2018; **378**(2):169–180.
2. **Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O.** Multiple sclerosis. *Lancet Lond. Engl.* 2018; **391**(10130):1622–1636.
3. **Lublin FD, Reingold SC, Cohen JA, et al.** Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014; **83**(3):278–286.
4. **Lublin FD, Coetzee T, Cohen JA, Marrie RA, Thompson AJ.** The 2013 clinical course descriptors for multiple sclerosis: A clarification. *Neurology.* 2020;10.1212/WNL.0000000000009636.
5. **Cree BAC, Mares J, Hartung H-P.** Current therapeutic landscape in multiple sclerosis: an evolving treatment paradigm. *Curr. Opin. Neurol.* 2019; **32**(3):365–377.
6. **Coles AJ, Twyman CL, Arnold DL, et al.** Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *The Lancet.* 2012; **380**(9856):1829–1839.
7. **Cohen JA, Coles AJ, Arnold DL, et al.** Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing–remitting multiple sclerosis: a randomised controlled phase 3 trial. *The Lancet.* 2012; **380**(9856):1819–1828.
8. **Cohen JA, Barkhof F, Comi G, et al.** Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* 2010; **362**(5):402–415.
9. **He A, Merkel B, Brown JW, et al.** Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol.* 2020; **19**(4):307–316.
10. **Harding K, Williams O, Willis M, et al.** Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis. *JAMA Neurol.* 2019; **76**(5):536–541.
11. **Saccà F, Lanzillo R, Signori A, et al.** Determinants of therapy switch in multiple sclerosis treatment-naïve patients: A real-life study. *Mult. Scler. J.* 2019; **25**(9):1263–1272.
12. **Ferraro D, Camera V, Baldi E, et al.** First-line disease-modifying drugs in relapsing–remitting multiple sclerosis: an Italian real-life multicenter study on persistence. *Curr. Med. Res. Opin.* 2018:1–12.
13. **Ferraro D, Camera V, Baldi E, et al.** First-line disease-modifying drugs in relapsing–remitting multiple sclerosis: an Italian real-life multicenter study on persistence. *Curr. Med. Res. Opin.* 2018:1–12.
14. **Elkjaer ML, Molnar T, Illes Z.** Teriflunomide for multiple sclerosis in real-world setting. *Acta Neurol. Scand.* 2017; **136**(5):447–453.
15. **Hersh CM, Love TE, Bandyopadhyay A, et al.** Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 24-month follow-up. *Mult. Scler. J. - Exp. Transl. Clin.* 2017; **3**(3):2055217317715485.
16. **Bermel RA, You X, Foulds P, et al.** Predictors of long-term outcome in multiple sclerosis patients treated with interferon β . *Ann. Neurol.* 2013; **73**(1):95–103.
17. **Río J, Rovira A, Tintoré M, et al.** Evaluating the response to glatiramer acetate in relapsing–remitting multiple sclerosis (RRMS) patients. *Mult. Scler. J.* 2014; **20**(12):1602–1608.

18. **Sormani MP, Gasperini C, Romeo M, Río J, Calabrese M.** Assessing response to interferon- β in a multicenter dataset of patients with MS. 2016;7.
19. **Río J, Castelló J, Rovira A, et al.** Measures in the first year of therapy predict the response to interferon β in MS. *Mult. Scler. J.* 2009; **15**(7):848–853.
20. **Tintore M, Rovira À, Río J, et al.** Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain J. Neurol.* 2015; **138**(Pt 7):1863–1874.
21. **Vukusic S, Casey R, Rollot F, et al.** Observatoire Français de la Sclérose en Plaques (OFSEP): A unique multimodal nationwide MS registry in France. *Mult. Scler. J.* 2020; **26**(1):118–122.
22. **Polman CH, Reingold SC, Banwell B, et al.** Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann. Neurol.* 2011; **69**(2):292–302.
23. **Patti F, Chisari CG, D’Amico E, et al.** Clinical and patient determinants of changing therapy in relapsing-remitting multiple sclerosis (SWITCH study). *Mult. Scler. Relat. Disord.* 2020; **42**:102124.
24. **Koch MW, Mostert J, Greenfield J, Liu W-Q, Metz L.** Gadolinium enhancement on cranial MRI in multiple sclerosis is age dependent. *J. Neurol.* 2020.
25. **Eden D, Gros C, Badji A, et al.** Spatial distribution of multiple sclerosis lesions in the cervical spinal cord. *Brain J. Neurol.* 2019; **142**(3):633–646.
26. **Brownlee WJ, Altmann DR, Alves Da Mota P, et al.** Association of asymptomatic spinal cord lesions and atrophy with disability 5 years after a clinically isolated syndrome. *Mult. Scler. Houndmills Basingstoke Engl.* 2017; **23**(5):665–674.
27. **Brownlee WJ, Altmann DR, Prados F, et al.** Early imaging predictors of long-term outcomes in relapse-onset multiple sclerosis. *Brain J. Neurol.* 2019; **142**(8):2276–2287.
28. **Arrambide G, Rovira A, Sastre-Garriga J, et al.** Spinal cord lesions: A modest contributor to diagnosis in clinically isolated syndromes but a relevant prognostic factor: *Mult. Scler. J.* 2017. Available at: <https://journals.sagepub.com/doi/10.1177/1352458517697830> [Accessed June 12, 2020].
29. **Malpas CB, Manouchehrinia A, Sharmin S, et al.** Early clinical markers of aggressive multiple sclerosis. *Brain J. Neurol.* 2020; **143**(5):1400–1413.
30. **Goodin DS, Reder AT, Ebers GC, et al.** Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFN β -1b trial. *Neurology.* 2012; **78**(17):1315–1322.

Figures legends

Figure 1: Cumulative proportion of patients switching for inefficacy. According to age (a), baseline EDSS (b), total number of relapses in the previous year (c) a,d presence of gadolinium enhancing lesions (d).

Figure 2: Cumulative probability of switch for inefficacy in patients who started a first-line therapy. The baseline factors were age (younger than 26 years), EDSS (higher than 2), presence of gadolinium enhancing lesions and number of relapses in the year preceding the treatment start (equal or higher than 2).

Tables :

Table 1 : Patients' characteristics at baseline.

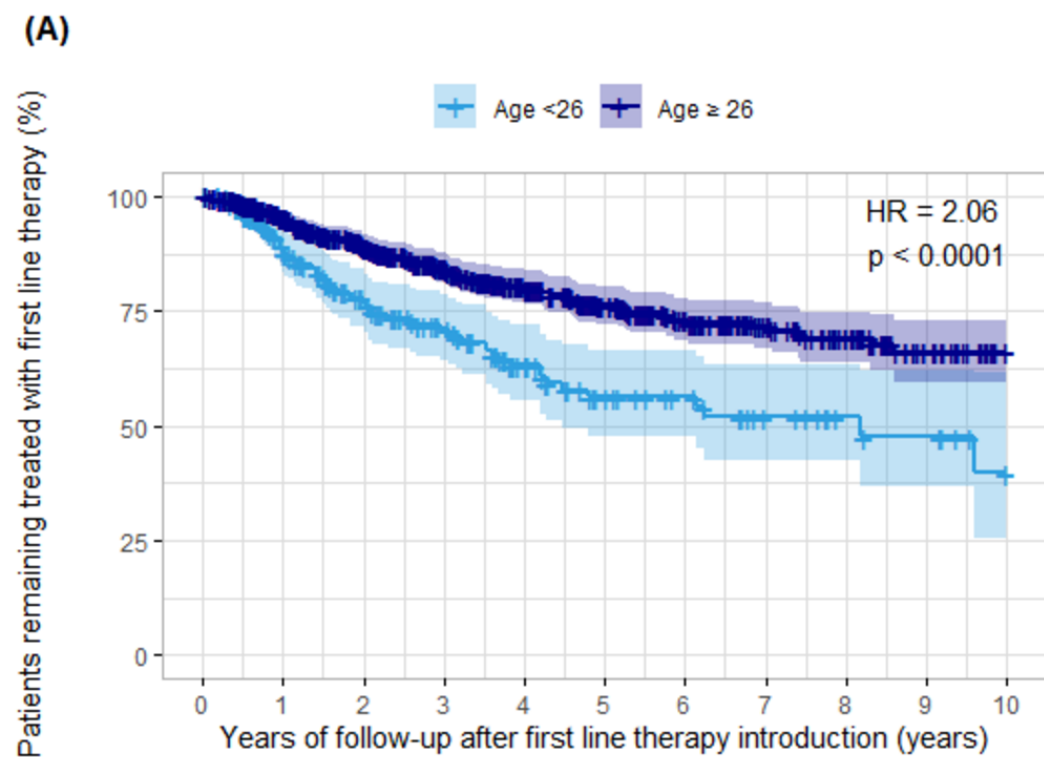
Clinical features	n	N=786 (with only switch for inefficacy vs No Switch)	Switchers (n= 185)	Maintainers (n= 601)
Age at treatment start, mean (SD), IQR	786	34.1 (10.3), 26-41	31.2 (9.4), 23-38	35.0 (10.4), 27-42
Women, n (%)	786	567 (72.14%)	128 (69.19%)	439 (73.04%)
Disease duration at treatment start, mean (SD)	786	1.0 (1.0)	1.0 (1.0)	1.1 (1.0)
Relapses in the previous year, mean (SD)	786	1.2 (0.7)	1.4 (0.8)	1.1 (0.7)
Relapses in the previous 2 years, mean (SD)	786	1.5 (0.8)	1.7 (0.8)	1.4 (0.8)
EDSS, mean (SD)	608	1.0 (1.1)	1.3 (1.2)	0.9 (1.1)
Follow-up, years (SD)	786	5.3 (3.2)	6.7 (3.1)	4.8 (3.1)
First line therapy, n (%)	786			
Interferon Beta		340 (43.3)	106 (57.3)	234 (38.9)
Glatiramer acetate	212 (24.57%)	192 (24.4)	40 (21.6)	152 (25.3)
Teriflunomide	139 (16.11%)	133 (16.9)	20 (10.8)	113 (18.8)
Dimethyl fumarate	130 (15.06%)	121 (15.4)	19 (10.3)	102 (17.0)
MRI findings				
Active lesion, yes, n (%)	663	413 (62.3)	109 (69.0)/ n=158	304 (60.2) n=505
>= 9 T2/FLAIR, yes, n (%)	585	457 (78.1)	107 (80.5)/ n=133	350 (77.4)/ n=452
Spinal cord lesions, yes, n (%)	520	389 (74.8)	97 (85.1)/ n=114	292 (71.9)/ n=406
Oligoclonal bands, yes, n (%)	528	492 (93.2)	119 (96.0)/ n=124	373 (92.3)/ n=404

Table 2: Univariate and multivariate Cox analyses of the prediction of treatment failure and therapeutic switch.

Variables	UNIVARIATE			MULTIVARIATE			MULTIVARIATE WITH MULTIPLE IMPUTATION		
	cHR	95% CI	p-value	AHR	95% CI	p-value	AHR	95% CI	p-value
Age (years)									
≥26	1	-	-	1	-	-	1	-	-
<26	2.19	[1.62 ; 2.97]	<0.001	2.24	[1.54 ; 3.26]	<0.001	2.19	[1.60 ; 3.00]	<0.001
Baseline EDSS									
<2	1	-	-	1	-	-	1	-	-
≥2	2.05	[1.56 ; 2.89]	<0.001	2.05	[1.42 ; 2.95]	<0.001	2.09	[1.46 ; 2.99]	<0.001
Relapses in the previous year									
nb<2	1	-	-	1	-	-	1	-	-
nb≥2	1.48	[1.10 ; 1.99]	0.009	1.51	[1.05 ; 2.16]	0.024	1.36	[1.01; 1.83]	0.046
Gadolinium enhancing lesions									
Absence	1	-	-	1	-	-	1	-	-
Presence	1.37	[0.98 ; 1.92]	0.064	1.28	[0.87 ; 1.88]	0.208	1.21	[0.85 ; 1.71]	0.296

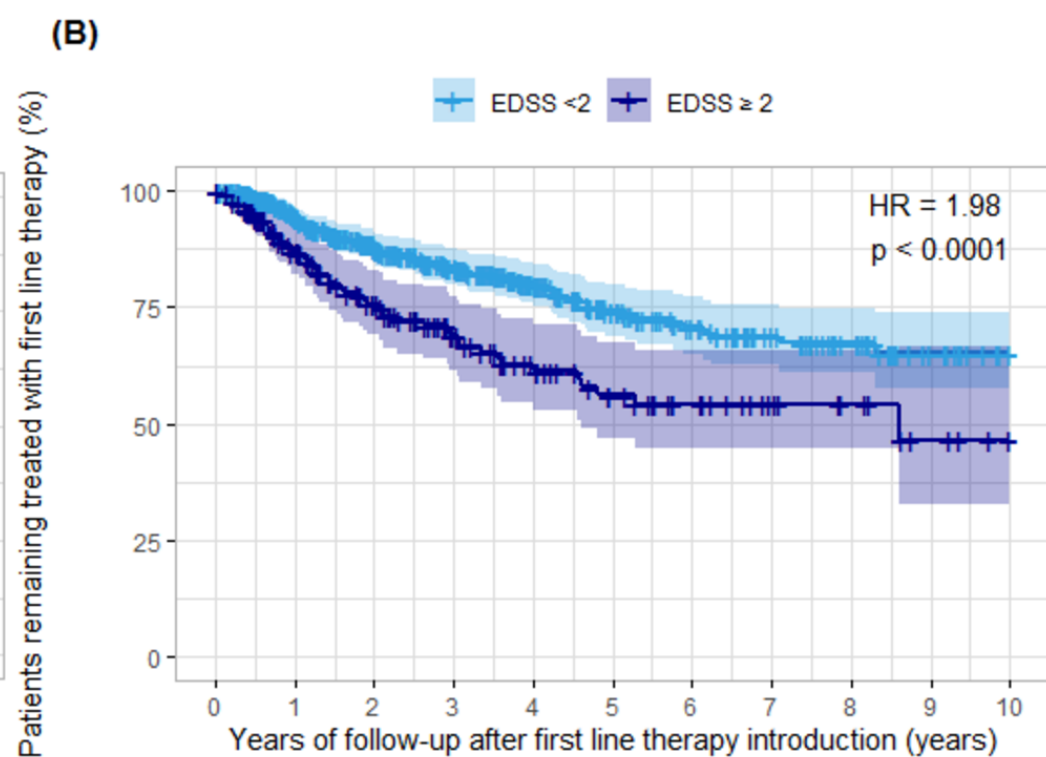
cHR : crude HR

AHR : adjusted HR



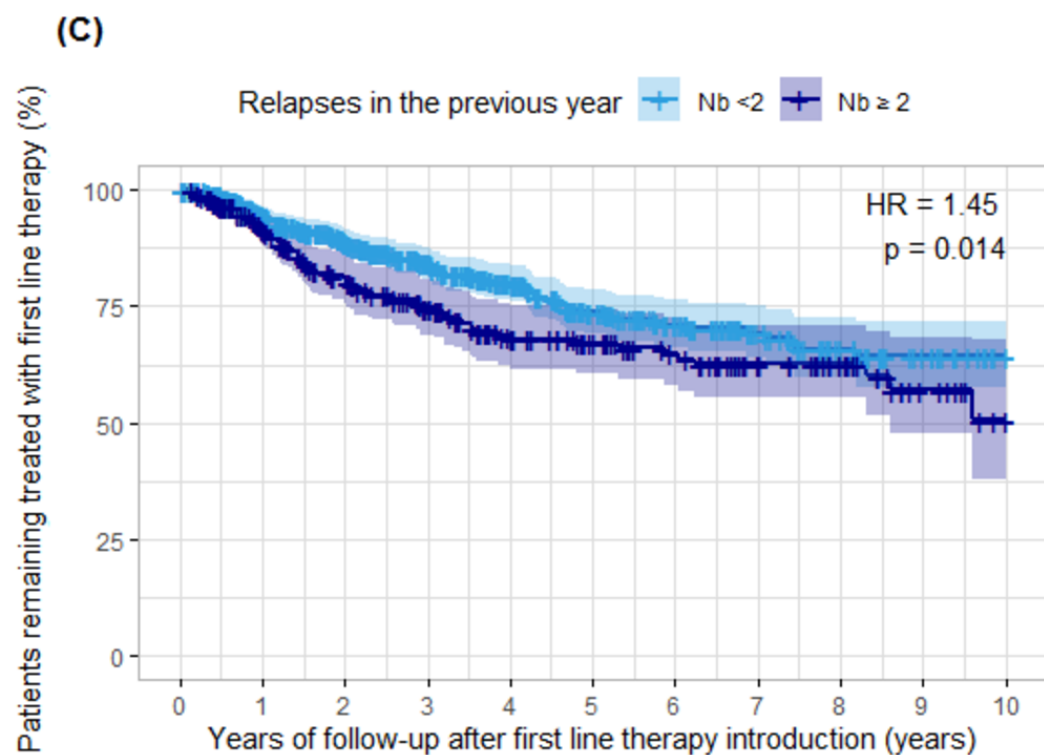
Patients at risk

	0	1	2	3	4	5	6	7	8	9	10
Age <26	206	152	111	82	52	34	27	18	12	10	5
Age ≥ 26	657	535	417	327	253	185	138	90	65	30	12



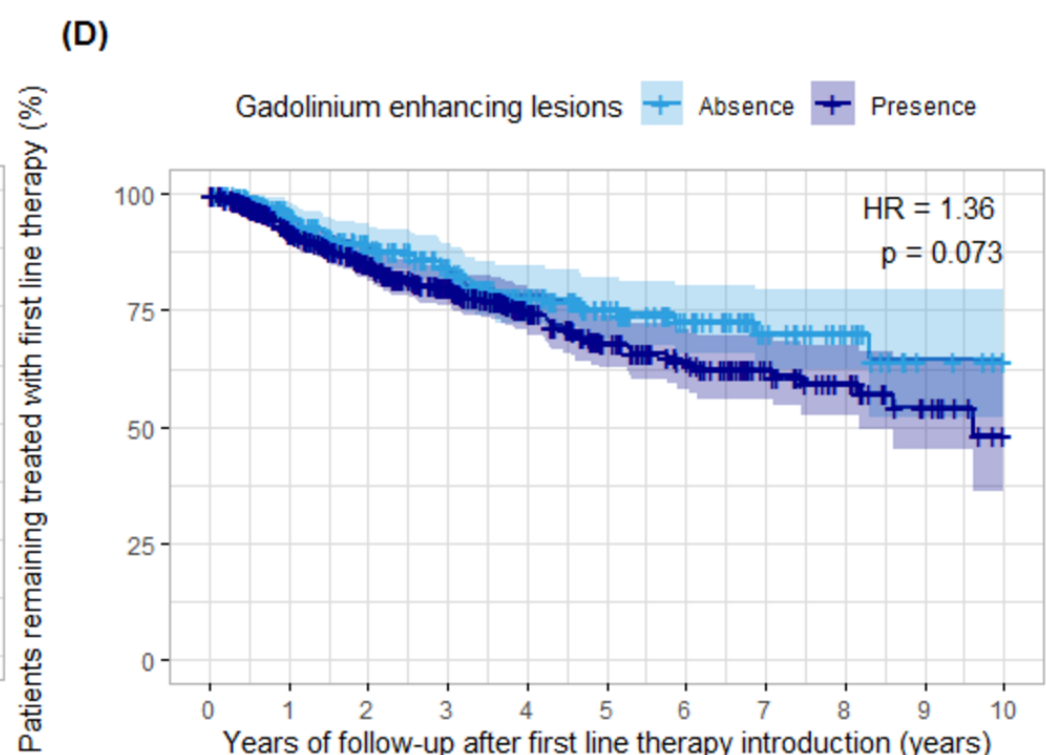
Patients at risk

	0	1	2	3	4	5	6	7	8	9	10
EDSS <2	490	371	276	213	151	99	75	52	37	19	8
EDSS ≥ 2	178	128	89	60	42	30	21	13	9	4	1



Patients at risk

	0	1	2	3	4	5	6	7	8	9	10
Nb <2	606	484	369	285	214	147	108	68	46	26	11
Nb ≥ 2	257	203	159	124	91	72	57	40	31	14	6

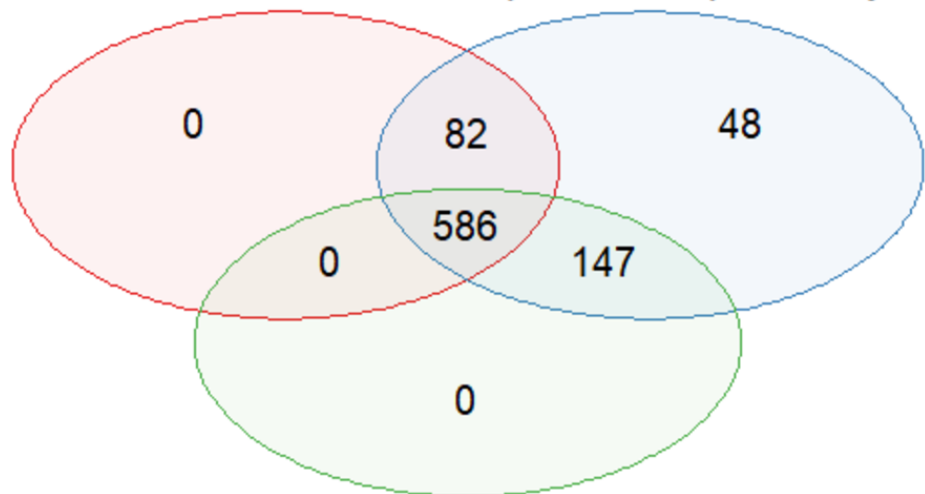


Patients at risk

	0	1	2	3	4	5	6	7	8	9	10
Absence	274	217	166	134	94	67	46	27	17	5	2
Presence	459	359	274	208	147	100	73	47	30	15	6

Baseline EDSS

Relapses in the previous year

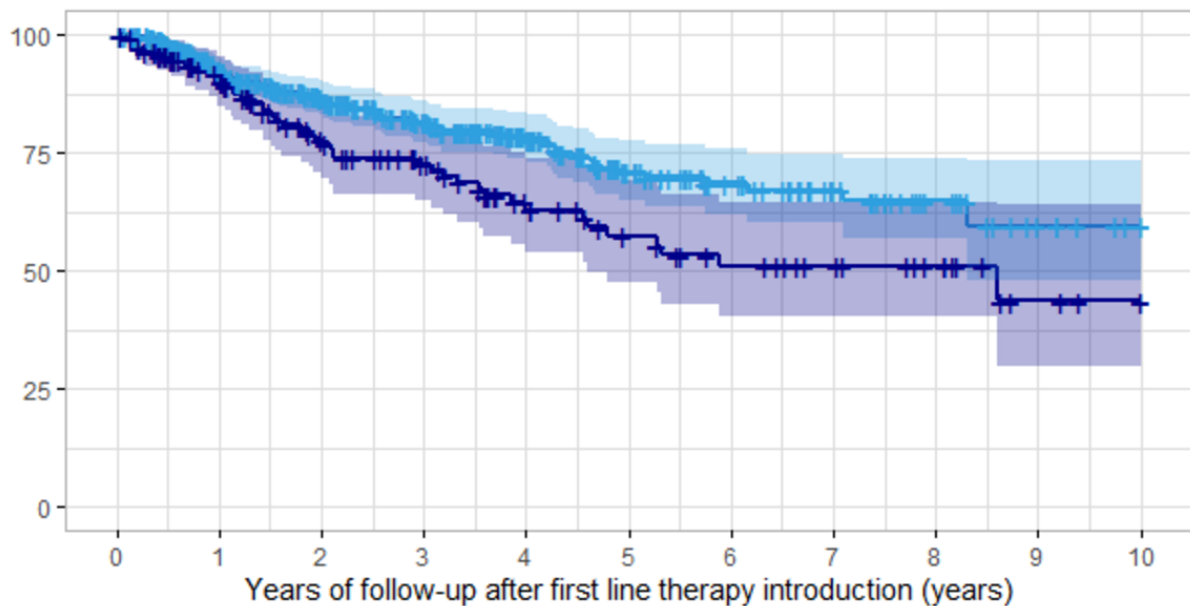


Gadolinium enhancing lesions

0

Patients remaining treated with first line therapy (%)

Nb of factors 0 or 1 or 2 3 or 4



Patients at risk

0 or 1 or 2

444 325 238 179 120 71 49 31 17 6 1

3 or 4

142 108 76 58 39 29 22 17 12 4 2