Age-dependent response to initial highly effective treatment in relapsing multiple sclerosis

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Key points

Question: Does the superiority of immediate initiation of highly effective (HE) disease-modifying treatments (DMTs) in relapsing multiple sclerosis (MS) persist in elderly patients?

Findings: This multicenter cohort study of 3.396 patients with relapsing MS found that the benefit of immediate HE-DMT initiation diminishes in patients over 45 years of age. However, prolonged exposure to DMTs, regardless of their efficacy level, reduced disability accumulation, demonstrating the overall effectiveness of DMTs even in this older age group.

Meaning: While DMT exposure helps protect MS patients from disability accumulation across all age groups, the advantage of immediate HE-DMT initiation tends to wane with age. Our findings help optimize the risk-benefit balance in elderly subjects with MS and assist clinicians and patients in making more personalized therapeutic decisions.

ABSTRACT

IMPORTANCE: Early initiation of highly effective (HE) treatment is increasingly favoured over the escalation approach in people with multiple sclerosis (MS), who are also experiencing increasing age with increasing life expectancy.

OBJECTIVE: To assess the impact of age on the superiority of HE disease-modifying treatments (DMTs) compared to platform DMTs in a real-world population of patients with relapsing MS.

DESIGN, SETTING, AND PARTICIPANTS: This cohort study utilized prospectively collected data from the Italian MS Register, including information from 82.197 patients across 77 Italian MS centres.

MAIN OUTCOMES AND MEASURES: The primary outcome was the occurrence of 24-week confirmed disability accumulation (CDA) events in patients treated with HE versus platform DMTs after 2 years from initiation and throughout the entire follow-up period.

EXPOSURES: Clinical and magnetic resonance imaging (MRI) characteristics, duration of exposure to DMT, either HE or platform.

RESULTS: After applying inclusion and exclusion criteria and conducting a 1:1 propensity score matching, the study evaluated 3,396 patients with MS (1.698 initiating HE DMTs, 1.698 initiating platform DMTs). After the first 2 years of follow-up, the proportion of CDA events was significantly lower in patients who started on HE DMTs (12.2%) compared to those on platform DMTs (15%), as confirmed by Cox regression analysis (HR=0.22, 95% CI 0.10-0.47; $p<0.001$). A significant interaction between age and HE DMTs was observed, indicating reduced effectiveness

of HE DMTs with increasing age (HR=1.50, 95% CI 1.11-2.03; p=0.008). The protective effect of HE DMTs was evident in patients under 45 years of age (HR=0.49, 95% CI 0.39-0.63; p<0.001) but was not observed in patients over 45 (HR=0.77, 95% CI 0.54-1.08, p=0.125). Similar findings emerged when assessing the risk of CDA over the entire follow-up period. Notably, prolonged exposure to any DMT during follow-up reduced disability accumulation even in patients over 45 years of age (HR 0.13, 95% CI 0.02-0.99; p=0.050).

CONCLUSIONS AND RELEVANCE: This real-world study of relapsing MS patients demonstrates that the benefit of immediate initiation of HE treatment diminishes with age, particularly after 45 years. However, even in this older age group, DMT exposure appears to reduce disability accumulation, indicating the overall effectiveness of DMTs regardless of their efficacy level, even beyond 45 years of age. It is however possible that, on an individual level, early HE treatment could still be more effective in this age group. Our findings help assist clinicians and patients in making more personalized therapeutic decisions.

INTRODUCTION

Recent epidemiological studies have shown an ever-growing prevalence of multiple sclerosis (MS) among the elderly, with peak-prevalence estimates occurring between the ages of 55 and 59 years;[1–6] moreover, a forward shift towards an older age at disease onset has been observed, possibly due at least in part to better case ascertainment and more sensitive diagnostic criteria and instruments.[7,8] This evolution in MS epidemiology poses unique challenges in disease management, as therapeutic decisions for elderly patients must take into account additional risk factors associated with frequent

comorbidities,[9] polypharmacy,[10] and immunosenescence,[11] the physiological aging of the immune system. On the other hand, data on the efficacy and safety of disease-modifying treatments (DMTs) in this age group are extremely limited. Indeed, evidence-based medicine in MS primarily stems from trials that have mostly enrolled subjects between 18 and 55 years of age, while real-world, registry-based data indicate that a large proportion of patients older than 60 years are still being treated.[12]

While ample evidence supports the superiority of early introduction of highly effective (HE) DMTs in relapsing MS,[13–16] whether this benefit is unaffected by aging remains an unresolved issue. Post-hoc analyses and meta-analyses of randomized controlled trials, as well as preliminary real-world evidence suggest a decreasing efficacy of HE-DMTs with increasing age.[17–20] Regarding safety, immunosenescence makes older people more vulnerable to infections[21–25] and malignancies,[26] particularly when treated with HE-DMTs. This increases the complexity of balancing the benefits and risks of more aggressive treatment approaches in elderly MS patients.

Against this background, using data collected within the Italian MS Register, we compared the risk of disability accumulation between immediate initiation of HE-DMTs and platform DMTs in a real-world cohort of relapsing MS patients, taking into account the effect of age at treatment onset. We hypothesized that aging could affect DMT effectiveness by reducing the benefit of early HE-DMT initiation compared to an escalation paradigm.

METHODS

Design

This cohort study used prospectively acquired data extracted from the Italian MS Register[27] on 30 November 2022. The Italian MS Register was approved by the Policlinico of Bari Ethics Committee and by the local ethics committees in all participating centers. Written informed consent was obtained from all enrolled patients in accordance with the Declaration of Helsinki. The minimum dataset required for this study comprised the main demographic characteristics, the date of disease onset, clinical course, follow-up visit dates, Expanded Disability Status Scale (EDSS)[28] scores recorded at each visit, the date of relapses, start and end dates of DMTs and DMT type. Quality assurance through online certification of EDSS competency is required at each participating site. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Patients

Patients with a clinically isolated syndrome (CIS) or relapsing-remitting (RR) course at the first neurological evaluation, a minimum of four visits with EDSS evaluation, a minimum of two-year follow-up and starting any DMT, either platform (interferons, glatiramer acetate, azathioprine, dimethyl fumarate, teriflunomide) or HE DMTs (natalizumab, anti CD20s, S1P modulators, cladribine, alemtuzumab, mitoxantrone) were included. We excluded patients with a primary or secondary progressive course at the first neurological evaluation and those enrolled in randomized controlled trials. The baseline was defined as the nearest visit within 120 days before or after the first DMT starting date; if baseline visits occurred within 30 days from a relapse, baseline was defined as the following assessment with EDSS scoring performed outside of a relapse and within 1 year from the first evaluation. When re-baseline was not possible, patients were excluded.
MS duration was calculated from the first demyelinating event. The follow-up time was defined as the time between baseline and last available EDSS evaluation. Confirmed disability accrual (CDA) was defined as ≥24-week confirmed disability increase from study baseline, measured by EDSS (increase ≥1.5 points if baseline EDSS = 0; increase ≥1.0 point if baseline EDSS ≥1.0 and ≤5.5;

increase ≥0.5 point if baseline EDSS ≥6.0). The date of CDA was assigned at the first EDSS score at which an increase occurred. For DMT exposure, the proportion of time during which patients received DMT was defined by the recorded starting and ending dates. The total time a patient spent on treatment was calculated including any switches and gaps in treatment. We did not consider gaps <3 months as a therapy interruption. For DMT in which extended treatment effects are recognized, the estimated treatment effect duration was used to calculate the proportion of time that patients received therapy (6 months for mitoxantrone, rituximab, ocrelizumab; 5 years for alemtuzumab and autologous haematopoietic stem-cell transplantation; 2 months for natalizumab; 12 months for cladribine).[29]

Statistical Analysis

Patients were matched on their Propensity Score (PS) of starting HE DMTs, with a 1:1 nearest neighbour matching ratio without replacement, within a caliper of 0.01 SD of the PS. Individual PS were calculated using a multivariable logistic model including the following covariates: sex, age, symptom at onset (multifocal versus monofocal), disease duration, disease course, EDSS score at baseline, number of relapses in the year before baseline.

The baseline and follow-up characteristics were expressed as mean and standard deviation (SD) or frequency and percentage for continuous and categorical covariates, respectively. Categorical and continuous variables were compared by using chi2 statistic, Mann–Whitney and Kruskal– Wallis tests, as appropriate.

Predictors of CDA events in HE vs platform DMTs after 2 years and the entire follow up were assessed through Cox regression models. The proportional hazard assumption was assessed through graphical inspections of residuals and scaled Schoenfeld residual test. In case of assumption violation, a time-dependent interaction was added to the model.[30] Cox regression models were adjusted for visit density and percentage of time spent on DMT before the event. To verify the dependency of HE DMT effectiveness on patient age, age (≤20; 20-40; 40-60; >60) and an

interaction term age (≤20; 20-40; 40-60; >60)*HE DMT were added. In case of significant interaction, predictors of CDA events in HE vs platform DMTs after 2 years and the entire follow up were further assessed in patients with baseline age ≤45 and >45. The cut-off of 45 years of age was selected on the base of available literature.[20,26]

Results of regression analyses were expressed as hazard ratio (HR) and 95% confidence interval (CI).

Two sensitivity analyses were performed: 1) including patients with baseline visit on or after the 1st January 2000; 2) including patients with brain/spinal MRI scan data available at baseline. In both cases, a new PS matching was applied with the same procedure as in the main analysis. In the sensitivity analysis with MRI data, baseline MRI activity (T1 gd enhancing lesions or new T2 lesions) was included among PS adjusting covariates.

All statistical analyses were performed with SPSS software, version 25.0 (SPSS inc.) and R, version 4.1.2 (R Foundation for Statistical Computing). A 2-sided P-value <0.05 was considered statistically significant.

Anonymized data, not published in the article, will be shared on reasonable request from a qualified investigator.

RESULTS

Data extraction was completed on 30th of November 2022. We had access to 82197 register patients from 77 Italian MS centers. By applying inclusion and exclusion criteria, we identified 20984 patients. After PS matching, our sample consisted of 3396 patients, of whom 1698 starting platform DMTs, and 1698 starting HE DMTs (Figure 1). Characteristics of the study sample before and after propensity score matching are depicted in Table 1. The matching procedure reduced the difference in PS between the two groups from 0,05 to 0,001, corresponding to a 98% improvement in the overall balance. The close match on individual characteristics was demonstrated by

standardized differences <10% for all matched characteristics (Table1). After the first 2 year follow-up, in the whole matched cohort (n=3396), 462 (13,6%) CDA events occurred, of which 208 (12,2%) in patients starting on HE DMTs, 254 (15,0%) in those starting on platform therapies (p=0,021). In the multivariable Cox regression analysis, starting on HE DMTs (HR=0,22, 95%CI 0,10-0,47; p<0,001) and longer exposure to any DMT before the event (HR=0,39, 95%CI 0,25-0,61); p<0,001) were associated with lower risk of CDA. On the other hand, older age at baseline was associated with higher risk of CDA (HR=1,35, 95%CI 1,10-1,65; p=0,004) (Table 2). The interaction between age and HE DMTs was significant, indicating reduced effectiveness of HE DMT with increasing age (HR=1,50, 95%CI 1,11-2,03; p=0,008).

Focusing on the subgroup of patients aged ≤ 45 years (n=2697; 1358 starting platform and 1339 starting HE DMTs) in the first 2 year follow up the proportion of CDA was significantly lower in patients starting on HE DMTs (136, 10,2% vs 183, 13,5%; p=0,008). In the multivariable Cox regression analysis, immediate treatment with HE DMTs (HR= 0,49, 95%CI 0,39-0,63; p<0,001) and longer exposure to any DMT before the event (HR=0,31, 95%CI 0,19-0,54; p<0,001) were associated with lower risk of CDA (Table 3).

Conversely, in the subgroup of patients aged > 45 years (n=699; 340 starting platform, 359 starting HE DMTs), the proportion of CDA in the first 2 years of follow up was not significantly different in the two groups (HE DMT 72, 20,1% vs platform 71, 20,9%; p=0,787), as confirmed in the Cox regression analysis (HR=0,77, 95%CI 0,54-1,08, p=0,125). A longer exposure to any DMT before the event was marginally associated with a lower risk of CDA in this age range, as well (HR 0,13, 95%CI 0,02-0,99; p=0,050) (Table 4).

The same Cox regression analyses were run over the entire follow up (8,6±5,3 years) and confirmed the previous results. In particular, starting on HE DMTs was associated with lower risk of CDA in the total sample (HR=0,40, 95%CI 0,26-0,62 p<0.001, eTable 1 in the Supplement) and in patients aged ≤ 45 years (HR=0,65, 95%CI 0,57-0,74; p<0,001, eTable 2 in the Supplement), The

association was no longer significant in patients aged > 45 years (HR=1,01, 95%CI 0,83-1,23; p=0,908, eTable 3 in the Supplement).

The two sensitivity analyses confirmed the main study findings (eTables 4-15 in the Supplement).

DISCUSSION

In this real-world, PS-matched cohort study, we found that the widely acknowledged superiority of immediate initiation of HE treatments compared to platform therapies in MS[13–16] tends to diminish with aging, particularly after the age of 45. This finding addresses a gap in RCTs, which primarily include patients aged 18-55 years, limiting the availability of data on treatment efficacy in "extreme" age ranges, such as children or adolescents and the elderly. Furthermore, our results align with preliminary evidence from post-hoc analyses of pivotal DMT trials[31–34] and a meta-analysis of RCTs[17], which demonstrate a decline in the ability to prevent disability accrual in patients older than 40-53 years. Additionally, initial evidence from real-world studies indicates a decrease in DMT efficacy with age,[19] along with a tendency for the advantage of HE over platform DMTs to diminish.[20]

A recently published paper showed a significant reduction in the annualized relapse rate and longer time to first relapse when using ocrelizumab compared to two platform therapies, interferon and glatiramer acetate, in patients over 60 years of age, without differences in confirmed disability progression.[35] We believe that the choice of outcome measures plays a significant role, particularly in this age group. It is well known that relapse activity in MS declines with increasing age.[36,37] Therefore, using relapse rate as a measure of clinical effectiveness of a DMT in older subjects might represent a less meaningful outcome. We feel that the use of disability accrual risk as the primary outcome represents a significant strength of our study. In this context, immediate initiation

of HE-DMTs did not reduce disability accumulation in patients older than 45 years, compared to a treatment escalation approach.

It should be noted, however, that even in patients over 45 years of age, longer exposure to any DMT, regardless of its efficacy level, was associated with a reduction in disability accrual. This finding marginally emerged in a previous real-world study. Specifically, Amato et al.[19] observed a trend towards sustained DMT efficacy in patients with late-onset MS. In another recent study involving MS patients over 50, the use of DMTs, and switching DMTs in the case of relapses, was associated with stability over active (relapsing), but not over progressive disease.[38]

Overall, these findings show that while prompt initiation of DMT remains a cornerstone of MS treatment, with increasing age, starting with a platform DMT (i.e., the escalating approach) could achieve effectiveness comparable to that of immediate initiation of HE-DMTs (i.e., the early aggressive approach). The early aggressive approach seems particularly suited for younger patients. In elderly MS patients, the introduction of HE-DMTs might be more appropriate after disease activity or disability accrual persist despite the use of platform DMTs. Whether a specific threshold of age exists at which this shift occurs, and which individual characteristics contribute to determine the subject response to treatments, remain open issues. The cut-off used in our study is based on a real-world study and a meta-analysis of RCTs, which demonstrated reduced efficacy[20] and higher risk of neoplasms[26] of HE-DMTs in patients over 45 years of age. However, it is possible that, on an individual level, early HE treatments could still be more effective than early platform DMTs in selected cases, even in those older than 45 years.

In this regard, our study suggests that traditional clinical and MRI features, such as EDSS disability level, relapse rate, and the presence of gadolinium-enhancing lesions or new/enlarging T2 lesions on MRI, may not be entirely appropriate markers in this age group. This may be partly due to the overall low inflammatory activity in advanced age and longer disease duration,[39–41] where

“smoldering” prevails on acute inflammation.[42] Therefore, identifying reliable biomarkers to distinguish the subgroup of older patients who could benefit from immediate initiation of HE-DMTs is needed. Potential candidates include more granular clinical measures, such as quantitative motor assessments[43] and neuropsychological tests,[44,45] laboratory biomarkers related to neurodegeneration,[46] such as neurofilament light chain[47] and glial fibrillary acidic protein[48] serum levels, and more advanced MRI features, such as slowly expanding lesions (SELs),[49,50] paramagnetic rim lesions (PRLs),[51] as well as quantitative measures of global and regional atrophy,[52,53] including cervical cord atrophy.[54]

Among MRI parameters, also the "brain age gap"—the difference between a patient's chronological age and the biological age of their central nervous system—appears to be a promising marker.[55] Other multidimensional indexes of biological age, which combine routine laboratory or instrumental analyses, such as the National Health and Nutritional Survey (NAHNES) biological age index,[56] have been recently used also in MS patients. It is possible to speculate that subjects with a greater brain age gap might derive less benefit from early initiation of HE-DMTs.

The results from our study are particularly relevant in the context of the growing body of evidence that raises safety concerns about exposing elderly MS patients to DMTs, particularly the HE ones.[57] Older age is associated with immunosenescence,[58] and also with increased individual frailty[59,60] due to the frequent coexistence of comorbidities[61] and polypharmacy.[62] These factors can increase the risk of severe adverse events from drug-drug interactions[63] and serious infections.[64] For instance, the risk of progressive multifocal leukoencephalopathy (PML) with natalizumab and dimethyl fumarate,[65] herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections and reactivations,[66] and anti-CD20 related hypogammaglobulinemia appear to increase with age.[67] Moreover, a recent meta-analysis of RCTs involving depleting agents in MS patients revealed a higher risk of developing neoplasms after the age of 45.[26]

The indication that platform DMTs may offer sufficient effectiveness in older MS patients supports a more personalized approach, potentially reducing the safety risks associated with more aggressive DMTs while maintaining comparable disease activity control. Furthermore, our results underscore the need for more evidence on de-risking strategies for DMT use in elderly MS patients, including de-escalation[68] or cessation strategies.[69]

In interpreting our findings some limitations should be considered. The evaluation of patients at baseline and follow-up was based solely on clinical assessments, as MRI data were only partially available at baseline. Nevertheless, a sensitivity analysis that included baseline MRI data from 1.934 patients confirmed the main results of our study. Additionally, we could not assess the absolute efficacy of DMTs due to the lack of a placebo arm. However, shorter exposure to any DMTs during the follow-up period was associated with a higher risk of disability accumulation. Moreover, the sample size of MS patients older than 45 years was relatively small, limiting our ability to capture slight differences in efficacy between HE and platform DMTs. Finally, we did not evaluate the safety of DMTs due to incomplete safety data available in the registry.

CONCLUSION

Our real-world study of relapsing MS patients indicates that the benefit of immediate initiation of HE treatments tends to diminish with age, particularly after 45 years. However, even in this age group, exposure to any DMTs, regardless of their efficacy level, is associated with a reduced risk of disability accumulation, confirming the overall effectiveness of DMTs in MS, even beyond 45 years of age. Nevertheless, on an individual basis it is possible that early HE treatment could be more effective also in this age group; further research focusing on imaging and fluid biomarkers is needed to identify those patients who may still benefit from a more aggressive treatment approach. Our findings help optimize the risk-benefit balance in elderly subjects with MS and assist clinicians and patients in making more personalized therapeutic decisions.

BIBLIOGRAPHY

1. Kingwell E, Van Der Kop M, Zhao Y, et al. Relative mortality and survival in multiple sclerosis: Findings from British Columbia, Canada. *J Neurol Neurosurg Psychiatry*. 2012;83(1):61-66. doi:10.1136/jnnp-2011-300616

2. Signori A, Schiavetti I, Gallo F, Sormani MP. Subgroups of multiple sclerosis patients with larger treatment benefits: A meta-analysis of randomized trials. *Eur J Neurol*. 2015;22(6):960-966. doi:10.1111/ene.12690

3. Grytten N, Aarseth JH, Lunde HMB, Myhr KM. A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland County, Western Norway. *J Neurol Neurosurg Psychiatry*. 2016;87(1):100-105. doi:10.1136/jnnp-2014-309906

4. Daltrozzo T, Hapfelmeier A, Donnachie E, Schneider A, Hemmer B. A Systematic Assessment of Prevalence, Incidence and Regional Distribution of Multiple Sclerosis in Bavaria From 2006 to 2015. *Front Neurol*. 2018;9. doi:10.3389/fneur.2018.00871

5. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology*. 2019;92(10):E1029-E1040. doi:10.1212/WNL.0000000000007035

6. Marrie RA, Yu N, Blanchard J, Leung S, Elliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. *Neurology*. 2010;74(6):465-471. doi:10.1212/WNL.0b013e3181cf6ec0

7. Koch-Henriksen N, Thygesen LC, Stenager E, Laursen B, Magyari M. Incidence of MS has increased markedly over six decades in Denmark particularly with late onset and in women. *Neurology*. 2018;90(22):e1954-e1963. doi:10.1212/WNL.0000000000005612

8. Prosperini L, Lucchini M, Ruggieri S, et al. Shift of multiple sclerosis onset towards older age. *J Neurol Neurosurg Psychiatry*. 2022;93(10):1137-1139. doi:10.1136/jnnp-2022-329049

9. Salive ME. Multimorbidity in Older Adults. *Epidemiol Rev*. 2013;35(1):75-83. doi:10.1093/epirev/mxs009

10. Hilmer S, Gnjidic D. The Effects of Polypharmacy in Older Adults. *Clin Pharmacol Ther*. 2009;85(1):86-88. doi:10.1038/clpt.2008.224

11. Liu Z, Liang Q, Ren Y, et al. Immunosenescence: molecular mechanisms and diseases. *Signal Transduct Target Ther*. 2023;8(1):200. doi:10.1038/s41392-023-01451-2

12. Zhang Y, Salter A, Jin S, et al. Disease-modifying therapy prescription patterns in people with multiple sclerosis by age. *Ther Adv Neurol Disord*. 2021;14. doi:10.1177/17562864211006499

13. He A, Merkel B, Brown JWL, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol*. 2020;19(4):307-316. doi:10.1016/S1474-4422(20)30067-3

14. Iaffaldano P, Lucisano G, Caputo F, et al. Long-term disability trajectories in relapsing multiple sclerosis patients treated with early intensive or escalation treatment strategies. *Ther Adv Neurol Disord*. 2021;14:175628642110195. doi:10.1177/17562864211019574

15. 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. doi:10.1001/jamaneurol.2018.4905

16. Filippi M, Amato MP, Centonze D, et al. Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. *J Neurol*. 2022;269(10):5382-5394. doi:10.1007/s00415-022-11193-w

17. Weideman AM, Tapia-Maltos MA, Johnson K, Greenwood M, Bielekova B. Meta-analysis of the age-dependent efficacy of multiple sclerosis treatments. *Front Neurol*. 2017;8(NOV). doi:10.3389/fneur.2017.00577

18. Jakimovski D, Eckert SP, Zivadinov R, Weinstock-Guttman B. Considering patient age when treating multiple sclerosis across the adult lifespan. *Expert Rev Neurother*. 2021;21(3):353-364. doi:10.1080/14737175.2021.1886082

19. Amato MP, Fonderico M, Portaccio E, et al. Disease-modifying drugs can reduce disability progression in relapsing multiple sclerosis. *Brain*. 2020;143(10):3013-3024. doi:10.1093/brain/awaa251

20. Vollmer BL, Wolf AB, Sillau S, Corboy JR, Alvarez E. Evolution of Disease Modifying Therapy Benefits and Risks: An Argument for De-escalation as a Treatment Paradigm for Patients With Multiple Sclerosis. *Front Neurol*. 2022;12. doi:10.3389/fneur.2021.799138

21. Amoriello R, Mariottini A, Ballerini C. Immunosenescence and Autoimmunity: Exploiting the T-Cell Receptor Repertoire to Investigate the Impact of Aging on Multiple Sclerosis. *Front Immunol*. 2021;12. doi:10.3389/fimmu.2021.799380

22. Persson R, Lee S, Ulcickas Yood M, et al. Infections in patients diagnosed with multiple sclerosis: A multi-database study. *Mult Scler Relat Disord*. 2020;41:101982. doi:10.1016/j.msard.2020.101982

23. Knapp R, Hardtstock F, Wilke T, et al. Comparing the risk of serious infections in patients with and without MS: A German claims data analysis. *Mult Scler Relat Disord*. 2023;72:104583. doi:10.1016/j.msard.2023.104583

24. Luna G, Alping P, Burman J, et al. Infection Risks among Patients with Multiple Sclerosis Treated with Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. *JAMA Neurol*. 2020;77(2):184-191. doi:10.1001/jamaneurol.2019.3365

25. Langer-Gould AM, Smith JB, Gonzales EG, Piehl F, Li BH. Multiple Sclerosis, Disease-Modifying Therapies, and Infections. *Neurology(R) neuroimmunology & neuroinflammation*. 2023;10(6). doi:10.1212/NXI.0000000000200164

26. Prosperini L, Haggiag S, Tortorella C, Galgani S, Gasperini C. Age-related adverse events of disease-modifying treatments for multiple sclerosis: A meta-regression. *Multiple Sclerosis Journal*. 2021;27(9):1391-1402. doi:10.1177/1352458520964778

27. Trojano M, Bergamaschi R, Amato MP, et al. The Italian multiple sclerosis register. *Neurological Sciences*. 2019;40(1):155-165. doi:10.1007/s10072-018-3610-0

28. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1444. doi:10.1212/WNL.33.11.1444

29. Kalincik T, Lizak N, Malpas CB, et al. Association of Sustained Immunotherapy with Disability Outcomes in Patients with Active Secondary Progressive Multiple Sclerosis. *JAMA Neurol*. 2020;77(11):1398-1407. doi:10.1001/jamaneurol.2020.2453

30. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival Analysis Part III: Multivariate data analysis - Choosing a model and assessing its adequacy and fit. *Br J Cancer*. 2003;89(4):605-611. doi:10.1038/sj.bjc.6601120

31. Miller AE, O'Connor P, Wolinsky JS, et al. Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis. *Multiple Sclerosis Journal*. 2012;18(11):1625-1632. doi:10.1177/1352458512450354

32. Hutchinson M, Kappos L, Calabresi PA, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: Subgroup analyses of AFFIRM and SENTINEL. *J Neurol*. 2009;256(3):405-415. doi:10.1007/s00415-009-0093-1

33. Turner B, Cree BAC, Kappos L, et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. *J Neurol*. 2019;266(5):1182-1193. doi:10.1007/s00415-019-09248-6

34. Zhang-Auberson L, Agoropoulou C, Häring DA, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fi ngolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. *Articles Lancet Neurol*. 2012;11:420-448. doi:10.1016/S1474

35. Foong YC, Merlo D, Gresle M, et al. Comparing ocrelizumab to interferon/glatiramer acetate in people with multiple sclerosis over age 60. *J Neurol Neurosurg Psychiatry*. Published online 2024. doi:10.1136/jnnp-2023-332883

36. Tremlett H, Zhao Y, Joseph J, et al. Relapses in multiple sclerosis are age- and time-dependent. *J Neurol Neurosurg Psychiatry*. 2008;79(12):1368-1374. doi:10.1136/jnnp.2008.145805

37. Scalfari A, Lederer C, Daumer M, Nicholas R, Ebers GC, Muraro PA. The relationship of age with the clinical phenotype in multiple sclerosis. *Multiple Sclerosis*. 2016;22(13):1750-1758. doi:10.1177/1352458516630396

38. Pfeuffer S, Wolff S, Aslan D, et al. Association of Clinical Relapses With Disease Outcomes in Multiple Sclerosis Patients Older Than 50 Years. *Neurology*. 2024;103(2). doi:10.1212/WNL.0000000000209574

39. Koch MW, Mostert J, Greenfield J, Liu WQ, Metz L. Gadolinium enhancement on cranial MRI in multiple sclerosis is age dependent. *J Neurol*. 2020;267(9):2619-2624. doi:10.1007/s00415-020-09895-0

40. Schwehr NA, Kuntz KM, Butler M, et al. Age-related decreases in relapses among adults with relapsing-onset multiple sclerosis. *Multiple Sclerosis Journal*. 2020;26(12):1510-1518. doi:10.1177/1352458519866613

41. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain*. 2006;129(Pt 3):606-616. doi:10.1093/brain/awl007

42. Giovannoni G, Popescu V, Wuerfel J, et al. Smouldering multiple sclerosis: the 'real MS.' *Ther Adv Neurol Disord*. 2022;15. doi:10.1177/17562864211066751

43. Kappos L, Wolinsky JS, Giovannoni G, et al. Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials. *JAMA Neurol*. 2020;77(9):1132-1140. doi:10.1001/jamaneurol.2020.1568

44. Jakimovski D, Weinstock-Guttman B, Roy S, et al. Cognitive Profiles of Aging in Multiple Sclerosis. *Front Aging Neurosci*. 2019;11. doi:10.3389/fnagi.2019.00105

45. Branco M, Ruano L, Portaccio E, et al. Aging with multiple sclerosis: prevalence and profile of cognitive impairment. *Neurological Sciences*. 2019;40(8):1651-1657. doi:10.1007/s10072-019-03875-7

46. Matthews PM. Chronic inflammation in multiple sclerosis — seeing what was always there. *Nat Rev Neurol*. 2019;15(10):582-593. doi:10.1038/s41582-019-0240-y

47. Disanto G, Barro C, Benkert P, et al. Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis. *Ann Neurol*. 2017;81(6):857-870. doi:10.1002/ana.24954

48. Meier S, Willemse EAJ, Schaedelin S, et al. Serum Glial Fibrillary Acidic Protein Compared With Neurofilament Light Chain as a Biomarker for Disease Progression in Multiple Sclerosis. *JAMA Neurol*. 2023;80(3):287-297. doi:10.1001/jamaneurol.2022.5250

49. Elliott C, Wolinsky JS, Hauser SL, et al. Slowly expanding/evolving lesions as a magnetic resonance imaging marker of chronic active multiple sclerosis lesions. *Multiple Sclerosis Journal*. 2019;25(14):1915-1925. doi:10.1177/1352458518814117

50. Preziosa P, Pagani E, Meani A, et al. Slowly Expanding Lesions Predict 9-Year Multiple Sclerosis Disease Progression. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(2). doi:10.1212/NXI.0000000000001139

51. Maggi P, Sati P, Nair G, et al. Paramagnetic Rim Lesions are Specific to Multiple Sclerosis: An International Multicenter 3T MRI Study. *Ann Neurol*. 2020;88(5):1034-1042. doi:10.1002/ana.25877

52. Miller DH, Barkhof F, Frank JA, Parker GJM, Thompson AJ. *Measurement of Atrophy in Multiple Sclerosis: Pathological Basis, Methodological Aspects and Clinical Relevance*.

53. De Stefano N, Stromillo ML, Giorgio A, et al. Establishing pathological cut-offs of brain atrophy rates in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2016;87(1):93-99. doi:10.1136/jnnp-2014-309903

54. Bischof A, Papinutto N, Keshavan A, et al. Spinal Cord Atrophy Predicts Progressive Disease in Relapsing Multiple Sclerosis. *Ann Neurol*. 2022;91(2):268-281. doi:10.1002/ana.26281

55. Cole PhD JH, Raffel MD J, Friede PhD T, et al. Longitudinal Assessment of Multiple Sclerosis with the Brain-Age Paradigm. *Ann Neurol*. 2020;88(1):93-105. doi:10.1002/ana.25746

56. Miner AE, Yang JH, Kinkel RP, Graves JS. The NHANES Biological Age Index demonstrates accelerated aging in MS patients. *Mult Scler Relat Disord*. 2023;77. doi:10.1016/j.msard.2023.104859

57. Macaron G, Larochelle C, Arbour N, et al. Impact of aging on treatment considerations for multiple sclerosis patients. *Front Neurol*. 2023;14. doi:10.3389/fneur.2023.1197212

58. Grebenciucova E, Berger JR. Immunosenescence: the Role of Aging in the Predisposition to Neuro-Infectious Complications Arising from the Treatment of Multiple Sclerosis. *Curr Neurol Neurosci Rep*. 2017;17(8). doi:10.1007/s11910-017-0771-9

59. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health*. 2018;3(7):e323-e332. doi:10.1016/S2468-2667(18)30091-4

60. Ayrignac X, Larochelle C, Keezer M, et al. Frailty in ageing persons with multiple sclerosis. *Multiple Sclerosis Journal*. 2021;27(4):613-620. doi:10.1177/1352458520923945

61. Marrie RA, Fisk JD, Fitzgerald K, et al. Etiology, effects and management of comorbidities in multiple sclerosis: recent advances. *Front Immunol*. 2023;14. doi:10.3389/fimmu.2023.1197195

62. Frahm N, Hecker M, Zettl UK. Polypharmacy among patients with multiple sclerosis: a qualitative systematic review. *Expert Opin Drug Saf*. 2020;19(2):139-145. doi:10.1080/14740338.2020.1720646

63. Debus JL, Bachmann P, Frahm N, et al. Associated factors of potential drug-drug interactions and drug–food interactions in patients with multiple sclerosis. *Ther Adv Chronic Dis*. 2022;13. doi:10.1177/20406223221108391

64. Buscarinu MC, Reniè R, Morena E, et al. Late-Onset MS: Disease Course and Safety-Efficacy of DMTS. *Front Neurol*. 2022;13. doi:10.3389/fneur.2022.829331

65. Prosperini L, de Rossi N, Scarpazza C, et al. Natalizumab-Related Progressive Multifocal Leukoencephalopathy in Multiple Sclerosis: Findings from an Italian Independent Registry. *PLoS One*. 2016;11(12):e0168376. doi:10.1371/journal.pone.0168376

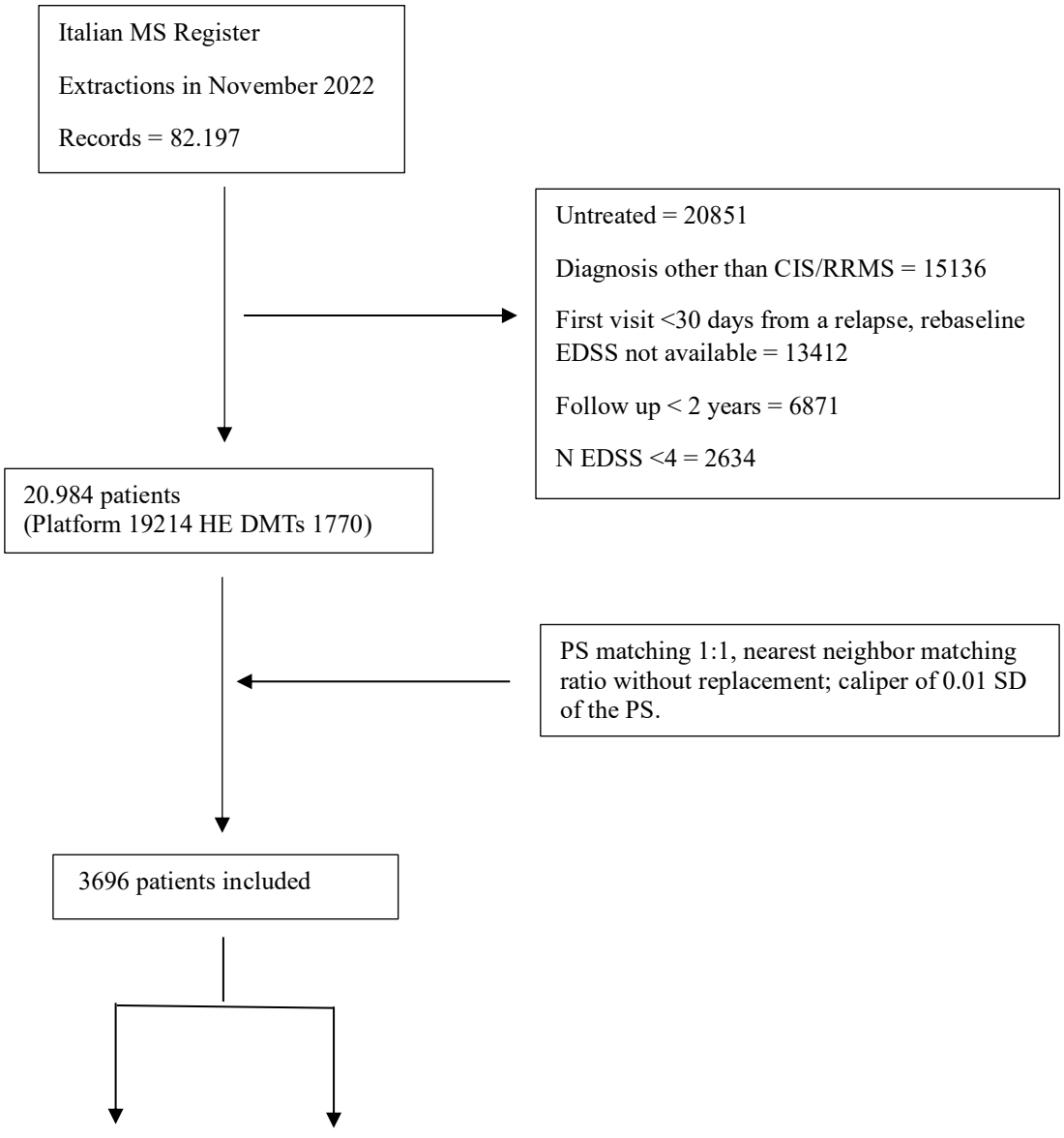
66. Havla J, Warnke C, Derfuss T, Kappos L, Hartung HP, Hohlfeld R. Interdisciplinary risk management in the treatment of multiple sclerosis. *Dtsch Arztebl Int*. 2016;113(51-52):879-886. doi:10.3238/arztebl.2016.0879

67. Sacco KA, Abraham RS. Consequences of B-cell-depleting therapy: Hypogammaglobulinemia and impaired B-cell reconstitution. *Immunotherapy*. 2018;10(8):713-728. doi:10.2217/imt-2017-0178

68. Vollmer TL, Nair K V., Williams IM, Alvarez E. Multiple Sclerosis Phenotypes as a Continuum: The Role of Neurologic Reserve. *Neurol Clin Pract*. 2021;11(4):342-351. doi:10.1212/CPJ.0000000000001045

69. Corboy JR, Fox RJ, Kister I, et al. Risk of new disease activity in patients with multiple sclerosis who continue or discontinue disease-modifying therapies (DISCOMS): a multicentre, randomised, single-blind, phase 4, non-inferiority trial. *Lancet Neurol*. 2023;22(7):568-577. doi:10.1016/S1474-4422(23)00154-0

FIGURE 1. Flow Diagram of the Study Sample.



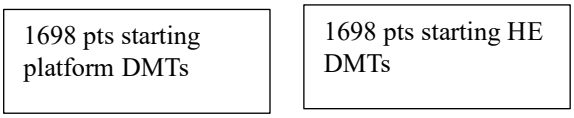


Table1. Demographic and Clinical Characteristics of the study sample before and after PS matching.

	TOTAL	UNMATCHED			MATCHED		
	n=20984	**PLATFORM (n=19214)**	**HE (n=1770)**	**SDM**	**PLATFORM (n=1698)**	**HE (n=1698)**	**SDM**
Sex, F, n (%)	14108 (67.2)	12968 (67.5)	1140 (64.4)	0.064	1100 (64.8)	1088 (64.1)	0.015
Age at baseline, mean (SD), years	36.0 (10.8)	36.1 (10.8)	35.2 (11.4)	-0.077	35.3 (10.7)	35.1 (11.4)	-0.014
Onset Topography, multifocal, n (%)	2456 (11.7)	2204 (11.5)	252 (14.2)	0.079	234 (13.8)	233 (13.7)	-0.002
Disease duration, mean (SD), years	5.1 (6.5)	5.2 (6.6)	4.1 (6.0)	-0.183	4.3 (5.7)	4.2 (6.0)	-0.025
EDSS at baseline, mean (SD)	1.9 (1.3)	1.9 (1.2)	2.6 (1.6)	0.469	2.5 (1.4)	2.5 (1.5)	-0.004
Disease course, n (%) **CIS** **RRMS**	 948 (4.5) 20036 (95.5)	 874 (4.5) 18340 (95.5)	 74 (4.2) 1696 (95.8)	0.018	 63 (3.7) 1635 (96.3)	 73 (4.3) 1625 (95.7)	-0.029
Relapses in the year before baseline, mean (SD)	1.0 (0.9)	1.0 (0.9)	1.2 (1.0)	0.207	1.2 (1.0)	1.2 (1.0)	-0.041

Abbreviations: HE, High Efficacy; SDM, standardized mean difference; F, female; SD, standard deviation; EDSS, expanded disability status scale; CIS, clinically isolated syndrome; RRMS, relapsing remitting multiple sclerosis

Table 2. Multivariable Cox Regression Model in the total sample after first 2 year follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.22	0.10-0.47	<0.001
Age at baseline	1.35	1.10-1.65	0.004
Age*HE DMT	1.50	1.11-2.03	0.008
Visit density [a]	1.66	1.59-1.74	<0.001
Percentage of time of follow up spent on DMT	0.39	0.25-0.61	<0.001

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

Table 3. Multivariable Cox Regression Model in patients ≤45 years of age after first 2 year follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.49	0.39-0.63	<0.001
Visit density [a]	1.70	1.61-1.79	<0.001
Percentage of time of follow up spent on DMT	0.31	0.19-0.54	<0.001

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

Table 4. Multivariable Cox Regression Model in patients >45 years of age after first 2 year follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.77	0.54-1.08	0.125
Visit density [a]	1.68	1.52-1.86	<0.001
Percentage of time of follow up spent on DMT	0.13	0.02-0.99	0.050

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable1. Multivariable Cox Regression Model in the total sample over the entire follow up (CDA events = 1438 (42.3%); 607 (35.7%) in HE DMT, 831 (48.9%) in platform; p<0.001)

	HR	95%CI	p value
HE vs platform DMTs	0.40	0.26-0.62	<0.001
Age	1.53	1.36-1.72	<0.001
Age*HE DMT	1.30	1.09-1.55	0.004
Visit density [a]	1.49	1.45-1.53	<0.001
Percentage of time of follow up spent on DMT	0.68	0.53-0.86	0.001

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable2. Multivariable Cox Regression Model in patients ≤45 years of age over the entire follow up (CDA events = 1024 (38%); 404 (30.2%) in HE DMT, 620 (45.7%) in platform DMT; p<0.001)

	HR	95%CI	p value
HE vs platform DMTs	0.65	0.57-0.74	<0.001
Visit density [a]	1.51	1.47-1.56	<0.001
Percentage of time of follow up spent on DMT	0.51	0.38-0.69	<0.001

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable3. Multivariable Cox Regression Model in patients ≥45 years of age over the entire follow up (CDA events = 414 (59.2%); 203 (56.5%) in HE DMT, 211 (62.1) in platform; p=0.138)

	HR	95%CI	p value
HE vs platform DMTs	1.01	0.83-1.23	0.908
Visit density [a]	1.49	1.41-1.57	<0.001
Percentage of time of follow up spent on DMT	1.27	0.83-1.96	0.275

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

SENSITIVITY ANALYSES

eTable4. Sensitivity analysis - MRI activity at baseline. Total sample (n=1934). 2year follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.71	0.55-0.92	0.009
Visit density [a]	0.44	0.38-0.51	<0.001
Percentage of time of follow up spent on DMT	0.72	0.35-1.48	0.370

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable5. Sensitivity analysis - MRI activity at baseline. Patients <45aa (n=1568). 2year follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.68	0.50-0.93	0.015
Visit density [a]	0.46	0.39-0.54	<0.001
Percentage of time of follow up spent on DMT	0.75	0.31-1.80	0.513

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable6. Sensitivity analysis - MRI activity at baseline. Patients >45aa (n=366). 2year follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.70	0.44-1.11	0.128
Visit density [a]	0.36	0.26-0.51	<0.001
Percentage of time of follow up spent on DMT	0.78	0.22-2.83	0.705

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable7. Sensitivity analysis - MRI activity at baseline. Total sample (n=1934). Entire follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.81	0.70-0.94	0.005
Visit density [a]	1.00	0.99-1.01	0.504
Percentage of time of follow up spent on DMT	0.99	0.99-1.00	0.010

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable8. Sensitivity analysis - MRI activity at baseline <45aa (n=1568). Entire follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.75	0.63-0.90	0.002
Visit density [a]	1.01	0.99-1.01	0.256
Percentage of time of follow up spent on DMT	1.27	0.81-1.99	0.302

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable9. Sensitivity analysis - MRI activity at baseline >45aa (n=366). Entire follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.97	0.73-1.29	0.832
Visit density [a]	1.00	0.99-1.02	0.552
Percentage of time of follow up spent on DMT	1.30	0.62-2.69	0.488

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable10. Sensitivity analysis – Diagnosis after 1st January 2000. Total sample (n=3348). Follow up 2 years.

	HR	95%CI	p value
HE vs platform DMTs	0.81	0.68-0.98	0.027
Visit density [a]	0.50	0.45-0.56	<0.001
Percentage of time of follow up spent on DMT	1.06	0.64-1.75	0.822

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable11. Sensitivity analysis – Diagnosis after 1st January 2000. Patients <45 years(n=2666). Follow up 2 years.

	HR	95%CI	p value
HE vs platform DMTs	0.76	0.61-0.95	0.017
Visit density [a]	0.49	0.44-0.56	<0.001
Percentage of time of follow up spent on DMT	0.81	0.45-1.47	0.489

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable12. Sensitivity analysis – Diagnosis after 1st January 2000. Patients >45 years (n=682). Follow up 2 years.

	HR	95%CI	p value
HE vs platform DMTs	0.88	0.63-1.22	0.431
Visit density [a]	0.55	0.44-0.67	<0.001
Percentage of time of follow up spent on DMT	2.01	0.81-5.34	0.126

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable13. Sensitivity analysis – Diagnosis after 1st January 2000. Total sample (n=3348). Entire follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.88	0.79-0.98	0.017
Visit density [a]	1.00	1.00-1.01	0.216
Percentage of time of follow up spent on DMT	0.99	0.77-1.28	0.938

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable14. Sensitivity analysis – Diagnosis after 1st January 2000. Patients <45 years (n=2666). Entire follow up.

	HR	95%CI	p value
HE vs platform DMTs	0.81	0.71-0.92	0.001
Visit density [a]	1.01	0.99-1.01	0.105
Percentage of time of follow up spent on DMT	0.96	0.70-1.31	0.773

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
a Adjusted for an interaction term with time

eTable15. Sensitivity analysis – Diagnosis after 1st January 2000. Patients >45 years (n=682). Entire follow up.

	HR	95%CI	p value
HE vs platform DMTs	1.05	0.86-1.28	0.632
Visit density [a]	1.01	1.00-1.02	0.056
Percentage of time of follow up spent on DMT	1.37	0.88-2.11	0.160

Abbreviations: HE, High Efficacy; DMT, Disease Modifying Treatment; HR, Hazard Ratio; CI, Confidence Interval.
[a] Adjusted for an interaction term with time