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Original Article

Disease-modifying therapies (DMTs) discontinuation in older relapsing-remitting multiple sclerosis (RRMS) patients with stable disease: Two-year randomized, controlled trial

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Abstract

Background: Disease-modifying therapies (DMTs) are the mainstay of relapsing-remitting multiple sclerosis (RRMS) treatment. Their efficacy decreases with age, while risks such as infections increase. This study aimed to evaluate the safety and clinical outcomes of DMT discontinuation in patients with RRMS aged 55 years and older.

Methods: We conducted a randomized clinical trial including 178 patients with RRMS aged ≥55 years, EDSS ≤3, and no relapses or MRI activity for at least 5 years. Patients were randomized to continue DMTs (n=89) or discontinue (n=89). Clinical relapses, EDSS scores, and MRI activity were assessed over 24 months.

Results: Relapses occurred in 9 (10.7%) patients in the continuation group and 12 patients (14.3%) in the discontinuation group (Risk Ratio [RR] = 1.33, 95% CI: 0.60 to 2.98; P=0.48). MRI activity was detected in 6 patients (7.1%) continuing DMTs and 9 (10.7%) patients who discontinued (RR = 1.50, 95% CI: 0.56 to 4.02; P=0.41). EDSS scores increased slightly in both groups during the first year. At 24 months, the mean EDSS was 1.59 (±0.74) in the continuation group and 1.36 (±0.74) in the discontinuation group, with no statistically significant difference between groups (mean difference = 0.23, 95% CI: -0.002 to 0.46; P=0.05).

Conclusion: In patients aged ≥55 years with stable RRMS, discontinuation of DMTs did not significantly increase relapses, disability progression, or MRI activity compared with continuation. These findings suggest that DMT discontinuation may be a safe and reasonable option for selected older patients. Larger, multicenter studies with longer follow-ups are warranted.

Keywords: Multiple sclerosis, Disease-modifying therapy, Recurrence, Aging, Disability.

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelination, axonal loss, and progressive neurological dysfunction (1). It is the most common non-traumatic cause of neurological disability in young adults, but the demographic profile of MS is shifting as both survival and life expectancy improve. Increasingly, neurologists are managing aging populations with MS, many of whom have been on long-term disease-modifying therapies (DMTs) (2). DMTs, including interferon-β, glatiramer acetate, teriflunomide, dimethyl fumarate, and monoclonal antibodies such as ocrelizumab and rituximab, reduce relapse rates and delay disability progression, especially in the early inflammatory phase of relapsing-remitting MS (RRMS) (3, 4). However, their long-term benefit in older patients is less clear. Immunosenescence, defined as the gradual decline of immune function with aging, leads to reduced inflammatory activity and fewer relapses in older individuals (5, 6).

This raises the possibility that continued immunosuppression may offer diminishing benefits while exposing patients to cumulative risks such as severe infections, malignancy, and progressive multifocal leukoencephalopathy (PML) (7, 8). Several observational studies suggest that the efficacy of DMTs decreases with age, with limited benefit beyond the age of 50–55 years (9, 10). Harding et al. reported that the therapeutic effect of DMTs on relapse risk declines steadily with age, becoming negligible in patients older than 53 (11). Conversely, the risk of adverse events, including opportunistic infections and malignancies, increases (12, 13). This has prompted debate over whether discontinuation of therapy in older, stable patients is reasonable. Despite growing interest in de-escalation strategies, prospective data are scarce. Most studies are retrospective and limited by selection bias (14). The DISCOMS trial, recently has reported, suggested that discontinuing DMTs in older patients did not substantially increase clinical risk, but evidence remains insufficient to guide practice (15). Therefore, this study aimed to evaluate the safety and clinical outcomes of DMT discontinuation in patients with RRMS aged 55 years and older with long-standing stable disease.

Methods

This randomized clinical trial enrolled patients aged >55 years with a confirmed diagnosis of MS according to the McDonald criteria. Participants were consecutively recruited and provided informed consent. Baseline demographic data were recorded, and patients were randomly assigned to the control or intervention group. The control group continued their existing disease-modifying drug (DMD) therapy, including oral agents (dimethyl fumarate, teriflunomide) or injectables (interferon beta-1a/1b, glatiramer acetate, rituximab, ocrelizumab). In the intervention group, prior DMD therapy was discontinued after study enrollment, and patients were closely monitored. Relapses prompted re-initiation of appropriate DMD therapy. All patients underwent baseline MRI and neurological assessment for EDSS scoring. Follow-up visits occurred every three months for EDSS assessment and relapse monitoring. Annual brain MRI was performed to detect new gadolinium-enhancing plaques or T2 lesions. Inclusion criteria were: RRMS patients with no relapses or new MRI lesions in the past five years, EDSS ≤3 with stable scores, current treatment with immunomodulatory therapy, and absence of major comorbidities. Exclusion criteria included refusal to participate, treatment with natalizumab or fingolimod (due to the risk of rebound after discontinuation of treatment with these drugs), recent MS diagnosis, or loss to follow-up. The patients were grouped into two groups based on the Balanced Block Randomization method: A and B. Both drugs (placebo and DMD drugs) were placed in boxes A and B, and only the physician responsible for implementing the plan (supervisor) was aware of the drug content of each group. In the intervention group, placebo was prepared, and in the control group, previous DMD drugs were prescribed to the patients. Then, the supervisor numbered each patient for use and noted in the notebook. The sample size was calculated based on a clinically relevant absolute difference in relapse rates derived from prior studies in older MS populations (16). Assuming a 10% difference in relapse proportions (e.g., 15% vs. 25%) between continuation and discontinuation groups, with a two-sided alpha of 0.05 and 80% power, a minimum of 89 patients per group was required. Thus, a total of 178 participants (89 per arm) were enrolled. Statistical analyses were performed in SPSS V22. Data normality was tested with the Kolmogorov–Smirnov test. Parametric (t-tests, ANOVA) or non-parametric (Mann–Whitney U, Kruskal–Wallis) tests were applied as appropriate, with $\alpha=0.05$. For the primary comparison of disability outcomes (EDSS scores) at 12 and 24 months, Analysis of Covariance (ANCOVA) was used to adjust for baseline EDSS scores, given the significant imbalance between groups at randomization. To assess the association between treatment group (continuation vs. discontinuation) and binary outcomes (e.g., relapse, new MRI activity) while controlling for potential confounding variables such as prior DMT class, binary logistic regression was employed. Adjusted odds ratios (aOR) with 95% confidence intervals are reported from these models. The threshold for statistical significance was set at $p < 0.05$.

Results

From an initial pool of 209 screened individuals, 31 patients were excluded prior to randomization (26 did not meet the inclusion criteria and 5 declined to participate). Consequently, 178 eligible patients were enrolled and randomized (89 to the continuation group and 89 to the discontinuation group). Following randomization, a final pre-intervention verification identified that five patients in the discontinuation group did not meet a specific inclusion criterion and were therefore withdrawn before the study intervention began. To maintain balanced group sizes for the final analysis and reduce potential bias, five patients from the continuation group, matched for age and baseline EDSS, were also randomly selected and excluded from the

per-protocol analysis. Thus, the final analysis included 84 patients in each group (total n=168). In the intervention group, 11 men and 73 women were enrolled compared with 15 men and 69 women in the control group (OR = 0.69, 95% CI: 0.30 to 1.60; P=0.72). A positive family history of MS was present in 16 patients in the control group and 12 in the intervention group (OR = 0.71, 95% CI: 0.31 to 1.61; P=0.16). The mean age was 59.25±2.46 years in the intervention group and 60.63±2.45 years in the control group (mean difference = -1.38 years, 95% CI: -2.14 to -0.62; P=0.32) (figure1).

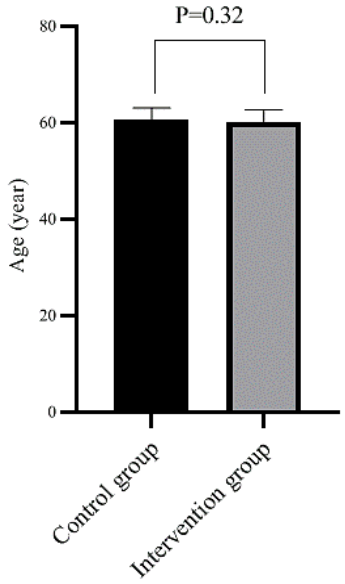

Figure 1. Mean age of patients in two groups

Mean disease duration was 21.63±5.54 years and 23.30±4.78 years, respectively (mean difference = -1.67 years, 95% CI: -3.40 to 0.06; P=0.058). At disease onset, symptoms included imbalance (11 vs. 8 patients; OR = 1.41, 95% CI: 0.53 to 3.78; P=0.49), paresthesia (38 vs. 39; OR = 0.96, 95% CI: 0.53 to 1.75; P=0.90), visual disturbances (20 vs. 17; OR = 1.20, 95% CI: 0.58 to 2.48; P=0.63), and limb paresis (15 vs. 20; OR = 0.73, 95% CI: 0.35 to 1.53; P=0.40) in the control and intervention groups, respectively. Paresthesia was the most frequent initial symptom in both groups (44% vs. 48%). Urinary symptoms were reported at onset by 54 patients (64%) in the control group and 41 (48%) in the intervention group (OR = 1.92, 95% CI: 1.04 to 3.54; P=0.64). All patients had brain plaques on MRI. Cervical cord lesions were observed in 44 control patients and 34 intervention patients (OR = 1.55, 95% CI: 0.88 to 2.75; P=0.13).

Regarding prior treatments, 19 control patients had received dimethyl fumarate, 15 glatiramer acetate, 22 interferons, 17 teriflunomide, and 11 rituximab. In the intervention group, the respective numbers were 9, 20, 29, 18, and 8. No significant difference was found between groups (P=0.21). Interferons were the most frequently used drugs in both groups (27% control, 35% intervention). Patients treated with fingolimod or natalizumab were excluded due to rebound risk after discontinuation.

During follow-up, 9 patients in the control group (10.7%) and 12 in the intervention group (14.3%) experienced relapses (RR = 1.33, 95% CI: 0.60 to 2.98; P=0.48). In the control group, relapses occurred in patients on dimethyl fumarate (n=2), glatiramer acetate (n=1), interferons (n=4), and teriflunomide (n=2). In the intervention group, relapses occurred in patients previously on dimethyl fumarate (n=1), glatiramer acetate (n=2), interferons (n=5), and teriflunomide (n=4). All relapsing patients were switched to rituximab, while others remained off immunomodulatory therapy. Relapses were most frequent among interferon users, consistent with higher baseline use. New gadolinium-enhancing lesions were observed in 6 (7.1%) control patients and 9 (10.7%), intervention patients with no significant difference (RR = 1.50, 95% CI: 0.56 to 4.02; P=0.41).

At baseline, mean EDSS was higher in the control group than in the intervention group (1.54±0.72 vs. 1.17±0.56, P=0.0004). To account for this baseline imbalance in the longitudinal analysis, an ANCOVA was performed, using the baseline EDSS score as a covariate. After adjustment for baseline scores, the control group had a significantly higher adjusted mean EDSS at one year (1.57, 95% CI: 1.45 to 1.69) compared to the intervention group (1.41, 95% CI: 1.29 to 1.53), with a mean difference of 0.16 (95% CI: 0.01 to 0.31; P=0.043). At two years, the difference in adjusted mean EDSS scores between the control (1.57, 95% CI: 1.44 to 1.70) and intervention (1.41, 95% CI: 1.28 to 1.53) groups was no longer statistically significant (mean difference = 0.16, 95% CI: 0.00 to 0.32; P=0.051). Overall, EDSS scores increased modestly during follow-up, reflecting relapses or disease progression, but remained stable after switching to rituximab (figure 2).

A logistic regression analysis was performed to assess the effect of treatment group on relapse risk while adjusting for the potential confounding effect of the prior DMT class. After adjustment, the odds of relapse in the discontinuation group were not significantly higher than in the continuation group (adjusted Odds Ratio [aOR] = 1.38, 95% CI: 0.60 to 3.18; P=0.45). Among prior DMTs, interferon was associated with a numerically higher, but not statistically significant, odds of relapse (aOR=2.30, 95% CI: 0.85 to 6.22; P=0.10) compared to dimethyl fumarate as the reference (table 1).

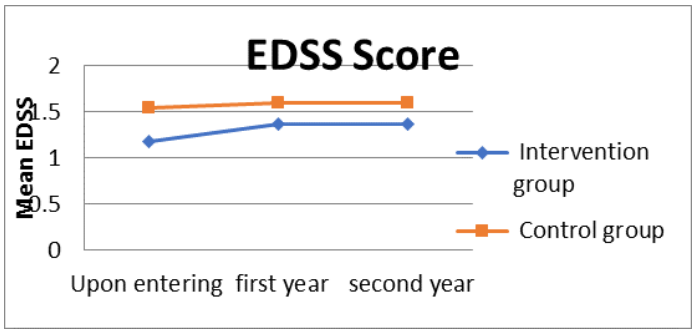

Figure 2. Mean EDSS scores in patients of the two groups

Table 1. Results of the adjusted logistic regression model for relapse outcome

Variable	Level	Adjusted Odds Ratio (aOR)	95% CI	P-value
Group (Intervention vs Control)		1.38	0.60 - 3.18	0.48
Prior DMT	Dimethyl Fumarate	1		
	Glatiramer Acetate	0.65	0.19 - 2.24	0.49
	Interferon	2.30	0.85 - 6.22	0.10
	Teriflunomide	2.28	0.73 - 7.07	0.15
	Rituximab	0.45	0.08 - 2.52	0.36

Discussion

Multiple sclerosis (MS) is a chronic neurological disease that causes demyelination and neurodegeneration, often leading to progressive and long-term disability. As its global prevalence rises, effective management strategies are increasingly important. Although disease-modifying therapies (DMTs) are central to treatment, their adverse effects can worsen clinical outcomes, especially in older patients. (3, 6). Age is a pivotal factor in therapeutic decision-making. Evidence suggests that patients over 50 years old may experience relapses if DMTs are discontinued, even in the presence of infection, highlighting the importance of individualized management to optimize prognosis and survival (9, 11). In this study, baseline characteristics were comparable between groups. The intervention group comprised 11 males and 73 females, and the control group included 15 males and 69 females (P=0.72), reflecting the higher prevalence of MS in women, consistent with epidemiological data (2, 3). Mean age was 59.3 years in the intervention group and 60.6 years in the control group (P=0.32), aligning with previous findings that older patients respond less effectively to DMTs and are more prone to adverse events (5, 6, 11, 12, 17). The mean disease duration was 21.6 years in the intervention group and 23.3 years in the control group (P=0.53), indicating that disease duration alone may not predict outcomes following DMT discontinuation (10, 14, 18). Family history of MS was positive in 14.3% of the intervention group and 19% of the control group (P=0.16), suggesting minimal impact on outcomes in older patients (6, 13, 19). Regarding clinical presentation, the most frequent initial symptom was paresthesia (48% in the intervention group, 44% in the control group), followed by visual disturbances, imbalance, and limb paresis. Multi-symptomatic urinary involvement was observed in 41 patients in the intervention group and 54 in the control group (P=0.64). These results are consistent with prior studies reporting paresthesia and visual symptoms as common early manifestations of RRMS, particularly in older adults (3, 6, 12, 20). MRI evaluations showed that all patients had brain lesions, while cervical lesions were present in 40.5% of the intervention group and 52.4% of the control group (P=0.12), indicating no significant effect of lesion location on outcomes after DMT discontinuation (7, 13, 21, 22). Relapse rates were 14.3% in the intervention group and 10.7% in the control group (P=0.48), suggesting that discontinuing DMTs does not necessarily increase relapse risk in older RRMS patients. EDSS scores increased modestly in both groups over two years (intervention: 1.17 → 1.36; control: 1.54 → 1.59; P=0.05), indicating that DMT discontinuation does not accelerate disability progression. These findings align with prior studies showing reduced DMT efficacy with advancing age and lower relapse risk in older patients (9, 11, 23, 24). Analysis by drug type revealed that relapses

were most frequent among patients receiving interferons, followed by teriflunomide, likely due to higher baseline usage. MRI activity, measured by Gd-enhancing lesions, did not differ significantly between groups (10.7% vs. 7.1%, P=0.41), suggesting that DMT discontinuation does not necessarily increase inflammatory activity in older patients (6, 12, 25, 26). Limitations of this study include the small sample size, limited follow-up of patients, and the non-participation of some MS patients who were being treated with high-risk DMDs. The findings of this study suggest that, within the precision limits of this trial, carefully monitored discontinuation of DMTs in selected older RRMS patients with long-term stable disease was not associated with a statistically significant increase in relapse risk or disability progression over 24 months. However, the modest sample size and low event rates result in wide confidence intervals that do not exclude a potentially clinically meaningful increase in risk. Therefore, treatment decisions should be individualized, weighing patient age, clinical status, disease activity, and the risk of adverse events. Larger prospective studies with longer follow-up are needed to provide more precise estimates of the long-term safety and outcomes of DMT discontinuation in this population.

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Availability of data and materials: All data pertaining to this study have been included in the manuscript. If you are interested in obtaining further information, please feel free to contact the corresponding author.

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References

1. Ghiasian M, Khazaei M, Daneshyar S, Khanlarzadeh E, Habibi MA. Oligoclonal band on the 5-year prognosis of patients with multiple sclerosis. Caspian J Intern Med 2025; 16: 288-4.
2. Zhang Y, Smith A, Lee H. Epidemiology of multiple sclerosis: Gender and age considerations. Neurol Clin 2020; 38: 289–303.
3. Macaron G, Campbell N, Mao-Draayer Y. Disease-modifying therapies in aging RRMS patients. J Neuroimmunol 2023; 379: 577690.
4. Shin J, Patel M, Duquette P, et al. Age-related decline in DMT effectiveness in RRMS. J Neurol Sci 2022; 434: 120141.
5. Weideman AM, Neuteboom RF, Uitdehaag BMJ, et al. Long-term disability outcomes in RRMS: impact of age and DMTs. Mult Scler 2017; 23: 124–35.
6. Ziemssen T, Sauer L, Ruck T. Disease course and treatment outcomes in elderly RRMS patients. Front Neurol 2022; 13: 812345.
7. Prosperini L, Mancinelli CR, De Giglio L, et al. MRI predictors of disease activity in older MS patients. J Neurol 2021; 268: 2124–33.
8. Alroughani R, Ahmed SF, Marafi D, et al. Safety and tolerability of long-term DMTs in older MS patients. Mult Scler Relat Disord 2021; 53: 103081.
9. Bsteh G, Hegen H, Ladstätter F, et al. Long-term outcomes after DMT discontinuation in MS patients. Mult Scler J 2020; 26: 1015–24.
10. Harding K, Williams O, Willis M, Robertson N. Efficacy of disease-modifying therapies in older adults with multiple sclerosis. Mult Scler Relat Disord 2019; 27: 283–9 .
11. Harding K, Williams O, Robertson N, et al. Age-dependent efficacy of disease-modifying therapies in MS: systematic review. CNS Drugs 2020; 34: 759–75.
12. Luna G, Alping P, Burman J, et al. Infection risk in older MS patients on immunomodulatory therapy. Neurology 2019; 92: e1497–e508.
13. Malpas CB, Boster AL, et al. Prognostic factors in elderly RRMS patients: clinical and MRI insights. Mult Scler Relat Disord 2022; 61: 103717.

14. Bsteh G, Di Pauli F, Hegen H, et al. Predictors of safe DMT discontinuation in MS patients. Mult Scler 2020; 26: 1225–34.
15. Corboy JR, Fox RJ, Cutter G, et al. DISCOntinuation of disease-modifying therapies in MS: The DISCOMS extension trial. Mult Scler 2025; 31: 159-73.
16. Comi G, Patti F, Rocca MA, et al. Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing–remitting multiple sclerosis: an 18-month, open-label, rater-blinded, randomised, multicentre study. J Neurol 2017; 264: 2436-49.
17. Zhu W, Xia Z. Treatment discontinuation in older people with multiple sclerosis. Curr Opin Neurol 2024; 37: 220-7.
18. Frau J, Schiavetti I, Landi D, et al. Treatment discontinuation in older patients with multiple sclerosis. Mult Scler Relat Disord 2025; 103: 106741.
19. Siddiqui A, Hua LH. Impact of Age on Switching or Stopping Disease Modifying Therapies in Multiple Sclerosis. Neurotherapeutics 2025; 22: e00603.
20. Shahid S, Hasan A, Iqbal M, et al. Discontinuation of disease-modifying therapy in stable multiple sclerosis: A systematic review and meta-analysis. Mult Scler Relat Disord 2025; 101: 106599.
21. Coerver EME, Fung WH, de Beukelaar J, et al. Discontinuation of first-line disease-modifying therapy in patients with stable multiple sclerosis: The DOT-MS randomized clinical trial. AMA Neurol 2025; 82: 123-31.
22. Gonzalez-Lorenzo M, Ridley B, Minozzi S, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev 2024; 1: CD011381.
23. Graves JS, Krysko KM, Hua LH, et al. Ageing and multiple sclerosis. Lancet Neurol 2023; 22: 66-77
24. Thakolwiboon S, Mills EA, Yang J, et al. Immunosenescence and multiple sclerosis: inflammaging for prognosis and therapeutic consideration. Front Aging 2023; 4: 1234572.
25. Jouvenot G, Courbon G, Lefort M, et al. High-efficacy therapy discontinuation vs continuation in patients 50 Years and older with nonactive MS. JAMA Neurol 2024; 81: 490-8.
26. Siddiqui A, Yang JH, Hua LH, Graves JS. Clinical and treatment considerations for the pediatric and aging patients with multiple sclerosis. Neurol Clin 2024; 42: 255-74.