Current Neurology and Neuroscience Reports (2024) 24:341–353
https://doi.org/10.1007/s11910-024-01355-w

REVIEW

# De-escalation and Discontinuation of Disease-Modifying Therapies in Multiple Sclerosis

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Accepted: 19 June 2024 / Published online: 12 July 2024


## Abstract

**Purpose of Review** Long-term use of multiple sclerosis (MS) disease-modifying therapies (DMTs) is standard practice to prevent accumulation of disability. Immunosenescence and other age-related changes lead to an altered risk–benefit ratio for older patients on DMTs. This article reviews recent research on the topic of de-escalation and discontinuation of MS DMTs.
**Recent Findings** Observational and interventional studies have shed light on what happens to patients who de-escalate or discontinue DMTs and the factors, such as age, treatment type, and presence of recent disease activity, that influence outcomes.
**Summary** Though many questions remain, recent findings have been valuable for the development of an evidence-based approach to making de-escalation and discontinuation decisions in MS.

**Keywords** DMT · De-escalation · Discontinuation · Aging · Immunosenescence

## Introduction

The field of multiple sclerosis (MS) has experienced enormous advances in the last 30 years, exemplified by the introduction of over 20 disease-modifying therapies (DMTs), which have been shown in large-scale clinical trials to reduce the occurrence of relapses and slow the accumulation of disability. An individual diagnosed with MS now faces a significantly lower risk of reaching disability milestones compared to 30 years ago [1]. A drawback of these therapeutic advances is that patients are in most instances committed to a treatment course that may last many years, even decades. While maintenance medication is common to many chronic conditions, there are certain factors unique to MS and MS DMTs that argue against the type of therapeutic inertia in which indefinite treatment is seen as the default approach [2]. Escalating costs [3], the inconveniences of administration and monitoring (and in the US at least, of obtaining insurance authorization), side effects, and safety concerns associated with DMTs are burdens largely borne by patients and their families. As all presently available DMTs act in some fashion on the immune system, persistent treatment may make patients vulnerable to infections or other complications—risks that may increase with treatment duration or to which older people are particularly susceptible [4, 5]. In addition, medical comorbidities and disability may accumulate as people age, heightening the risks associated with certain DMTs. The COVID-19 pandemic was a wake-up call to many MS patients and their healthcare providers, putting into sharp relief the underappreciated dangers of a compromised immune system, and leading some to put DMTs on hold, temporarily or permanently. Older age [6, 7], greater levels of disability, and by some accounts certain MS DMTs [8, 9] were associated with worse outcomes in COVID-19 registries of MS patients, though COVID-19-associated morbidity and mortality have decreased since the early days of the pandemic.

Although some amount of risk may be unavoidable and outweighed by the advantages of DMT use, evidence from observational studies and interventional trials have shown that DMTs confer their greatest benefit in the first few years after disease onset, when overt signs of inflammation (relapses and new or active lesions on neuroimaging) occur with greatest frequency. Sub-group analyses from clinical trials of multiple MS DMTs show diminished efficacy in older age groups [10] (also reviewed by Jakimovski et al.

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[11] and Macaron et al. [12]). Despite the fact that about half of all people with MS in the US are at least 55 years of age, clinical trials of MS DMTs have mostly used an upper age limit of 55 in relapsing–remitting multiple sclerosis (RRMS), or up to 60 or 65 in some secondary progressive (SPMS) trials, thus limiting the conclusions one can draw about DMT safety and efficacy in older populations. With that caveat, a meta-analysis of DMT clinical trials involving 38 clinical trials and over 28,000 participants estimated that the average patient over age 53 does not benefit from DMT use in terms of disability progression [13]. Given the possibility of higher risk and lower benefit in older age and after years of DMT use, it is appropriate to ask whether continued treatment with expensive and potentially risky DMTs is in the best interest of some patients (not to mention health systems [14]). Doctors and patients are of course already making discontinuation decisions everyday: in MS studies involving large registries and healthcare claims databases, DMT use is consistently greater in younger patients compared to their older counterparts, many of whom presumably discontinued their DMT at some point (though others may have never been treated) [15–17]. Certainly, many MS providers can recall patients who have discontinued a DMT and remained stable at follow up visits. But when is it safe and appropriate for the neurologist to recommend permanent DMT discontinuation? What attributes of the patient, or of the treatment, suggest a higher likelihood of stability upon DMT discontinuation? Given the reluctance of many patients to discontinue a DMT altogether [18], are there safer or better tolerated strategies to de-escalate treatment, such as tapering the dose or extending the interval between treatments? This review aims to critically evaluate the literature of MS DMT discontinuation and de-escalation, introducing the reader to the different approaches to treating patients with MS over their lifetimes, exploring the concepts of aging and immunosenescence in MS, and examining outcomes from a variety of clinical studies on this topic. Where the evidence is murky or expert views diverge, we offer our opinion, recognizing that more research in this area is needed.

## DMTs in Early Disease Course: Escalation vs Induction vs High-Efficacy Therapy

With more DMT options currently available and increasing recognition that disability accumulation frequently occurs independent of relapses (progression independent of relapse activity, or PIRA), even early in the course of MS and in the relapsing–remitting phase [19, 20], the initial choice of DMT is more important than ever. Evidence from multicenter cohort studies and population-based registries demonstrate that early initiation of high-efficacy DMTs appears to lead to better functional outcomes compared to lower efficacy DMTs, particularly in relapse-onset MS (these data largely predated the widespread use of high efficacy DMTs in primary progressive MS) [21–25]. Yet there remains some controversy about the optimal treatment algorithm for newly diagnosed patients, with some emphasizing an escalatory approach and others arguing for early use of high-efficacy DMTs [26, 27]. In the initial selection of DMT, drug availability may be limited by geographic location, regulatory structures, or payer authorization; patients may worry about the risk of possible adverse events; or prescribing options may simply be dictated by provider familiarity or risk aversion.

The need or desire to consider treatment de-escalation is frequently influenced by the specific DMT being used. One example of this is switching from natalizumab due to an increasing risk of progressive multifocal leukoencephalopathy (PML) with prolonged use [28] (more on this below). Some leukocyte-depleting MS DMTs also have a dose-dependent risk of toxicity (e.g. mitoxantrone, cladribine), so discontinuation or de-escalation becomes imperative. The decision to re-treat after an induction phase with a pulsed immune reconstitution therapy like alemtuzumab or cladribine may depend on whether disease reactivation has occurred [29, 30]. For example, in analysis of long-term outcomes of patients in the CLARITY/CLARITY Extension studies of cladribine, 46.9% (204/435) of participants had subsequent DMT use, mainly in the form of a platform DMT, at a median of 10.9 years since their last dose [31]. Similarly, while hematopoietic stem cell transplantation (HSCT) seemed to offer the promise of "one and done" with high rates of No Evidence of Disease Activity (NEDA) and event-free survival, some patients have nevertheless required subsequent DMT resumption [32]. By contrast, most traditional immunotherapies including glatiramer acetate, interferon β formulations, the fumarates (dimethyl fumarate, monomethyl fumarate, and diroximel fumarate), sphingosine-1-phosphate receptor (S1PR) modulators (fingolimod, siponimod, ozanimod, ponesimod), natalizumab, and anti-CD20 immunotherapies (rituximab, ocrelizumab, ublituximab, ofatumumab) require persistent administration to maintain efficacy. In the absence of safety or tolerability concerns, these DMTs might be continued for many years.

## Aging and Immunosenescence in MS

Immunosenescence is defined as the age-related weakening of adaptive and innate immune systems including the differentiation and maturation of different immune subsets, immune cell functionality, and responsiveness to vaccinations [33–37]. Senescent immune cells change their secretory pattern to produce a more pro-inflammatory milieu (so-called "senescence-associated secretory phenotype" or SNAP), which in combination with accumulated cellular

debris and self-antigens can lead to "inflammaging"—the low-grade inflammation present in older age that can contribute to tissue damage and degenerative diseases [33–37]. Alterations in B and T cell subsets, reduced diversity of B and T cell receptors, and diminished antibody production take place in older age, which helps to explain why extra vaccinations or higher vaccine doses are sometimes recommended in older populations. For example, in a single-center cohort study, reduced humoral response to hepatitis B vaccination was observed in older patients with MS, who were more likely to require a 4th vaccine dose to achieve seroprotection [38]. Aging resident central nervous system cells, such as astrocytes and microglia, lose their homeostatic functions and shift their secretory patterns toward a more pro-inflammatory profile [39, 40]. Remyelination efficiency diminishes with age as a result of failure of oligodendrocyte precursor cell recruitment and differentiation [41–43], which may be why older age is associated with worse recovery from MS relapses [44].

Age is the most consistently recognized modifier of MS disease course [33, 45]. Relapse rates are highest in the early years of the illness and seen at higher frequencies in pediatric MS than in adult-onset MS, and lowest rates in late-onset MS (with corresponding least to greatest proportions of primary progressive MS presentations in these age groups) [46–49]. After years of chronic inflammation and loss of neurological reserve, some relapse-onset MS patients transition to secondary progressive MS [45, 50, 51]. Atrophy occurs at an accelerated rate throughout the course of MS [52], though the MS-specific contribution wanes over time, specifically for whole brain and thalamic atrophy, while the contribution of normal aging to volume loss increases [53]. Consistent with these clinical and imaging observations, studies demonstrate evolution of pathological changes as patients age with MS [54–56]. The infiltration by B and T lymphocytes and formation of white matter plaques early in the disease process gives way to slow expansion of pre-existing lesions and gradual lymphocyte accumulation in connective tissue spaces of the brain such as the meninges and Virchow Robin spaces, while blood–brain barrier disruption subsides over time (seen on magnetic resonance imaging [MRIs] as reduced gadolinium-enhancing lesions with aging [57]). Age-associated changes in sex hormones, such as declines in testosterone levels in men and anti-Mullerian hormone in perimenopausal women, have been linked to brain atrophy and risk of disability progression in patients with MS, respectively [33].

Relative to controls, people with MS (particularly progressive MS) are at higher risk for infections and infection-associated hospitalizations, independent of DMTs, with absolute infection rates highest in the oldest age groups [58, 59]. Complicating this, use of MS DMTs, especially more immunosuppressive ones, can become riskier with longer use and in older individuals. As mentioned above, natalizumab-associated PML rates increase with longer treatment, particularly for those who test positive for antibodies to the JC virus [28]. JC virus seropositivity has been shown to increase with age [60]. In a study of the first 336 confirmed post-marketing cases of natalizumab-associated PML, older patients had a higher mortality [61], similar to what was found in a French population-based study of all PML cases from any cause over a 10-year span [62]. Meta-analyses of PML in MS have found earlier PML onset and worse outcomes in older patients [63, 64]. Prior to the availability of JC virus serological testing, many chose to de-escalate from natalizumab at the 2-year mark (after which PML risk rises faster), though our present practice is typically to continue natalizumab treatment beyond this point as long as the serum JC virus antibody remains negative with regular (e.g. at least every 6 months) blood monitoring. De-escalation from natalizumab, after JC virus seroconversion for example, was previously necessitated by the limited number of high efficacy alternatives; now with the availability of other effective options that carry lower risk of PML, "lateral moves" after natalizumab are possible.

Common medical co-morbidities such as diabetes, hypertension, and cardiac arrythmias become more prevalent in older individuals, potentially raising the risk for complications from fingolimod, for example. Though analysis of clinical trial data from 11 ocrelizumab clinical trials demonstrates an acceptable safety profile with up to 7 years of treatment [65], real world data suggest a higher risk of infections with B cell depletion with than other MS DMTs [66, 67]. Risk of infection increases with longer use of anti-CD20 immunotherapies and with hypogammaglobulinemia, itself a consequence of prolonged use of these DMTs [4, 68]. Wheelchair-bound patients taking rituximab are particularly susceptible to infections [4]. Whether newer anti-CD20 DMTs, such as ublituximab and ofatumumab, will face similar issues remains to be seen.

Certain MS DMTs impair the normal response to vaccinations, which may become increasingly important as people age (see Table 1). In a 2012 review of vaccinations in MS, the authors noted that large-scale and prospective studies of vaccinations with MS DMTs were scarce [69]. Studies have emerged to suggest largely preserved vaccine responses with interferon β, teriflunomide, alemtuzumab, and the fumarates, variably diminished responses with glatiramer acetate, and inadequate responses to various vaccinations with S1PR modulators, natalizumab, and anti-CD20 DMTs [38, 70–75]. Findings from a meta-regression of 45 MS clinical trials identified an age-dependent risk of neoplasm with use of depletive agents (alemtuzumab, cladribine, and ocrelizumab), particularly for patients older than 45 years [76]. Periodic reassessments of the DMT risk–benefit ratio

**Table 1** Comparison of DMT efficacy and side effects

| | Efficacy | Side effects | PML risk | Rebound risk? | Reduced vaccination response |
|---|---|---|---|---|---|
| Interferon β | + | Injection reactions, flu-like symptoms | - | No | - |
| GA | + | Injection reactions, lipoatrophy | - | No | ± |
| Teriflunomide | + | Hair loss, paresthesias, liver dysfunction | - | No | ± |
| S1P modulators (eg fingolimod) | + + | Headache, back pain, shingles, infections | + + | Yes | + + |
| Fumarates (eg dimethyl fumarate) | + + | GI upset, flushing | + | No | - |
| Cladribine | + + | Infections, malignancy | +* | No | ? |
| Natalizumab | + + + | PML | + + + | Yes | + |
| Anti-CD20 (eg ocrelizumab) | + + + | Infusion reactions, infections, hypogammaglobulinemia | + | No | + + + |
| Alemtuzumab | + + + | Infusion reactions, infections, secondary autoimmune conditions | + | No | ± |

*PML not yet observed with cladribine for MS but has been reported when used for other indications

in older individuals based on their unique risk factors would allow for a more personalized approach to care.

## Discontinuation and De-escalation

### Discontinuation

In 2018, the American Academy of Neurology issued practice guideline recommendations on MS DMTs, including a discussion of when to consider DMT discontinuation, but given the paucity of data in this area stopped short of making firm recommendations except for those with SPMS without recent disease activity and an Expanded Disability Status Scale (EDSS) of at least 7—unable to walk more than 5 m, largely restricted to a wheelchair— for 2 years (Level B) [77]. In an ideal world, patients contemplating DMT discontinuation would discuss the pros and cons with their neurologist before taking the leap. In the real world, these decisions are sometimes made independently by the patient and disclosed to the neurologist afterward (or not at all if the patient never returns). Treatment interruptions can occur as an intended step between two different DMTs (or for family planning purposes) and thus should be distinguished from a planned permanent discontinuation, though studies have historically not always made this distinction. (Discussion of DMTs and pregnancy is outside the scope of this review but is available elsewhere [78].) Patients choose to discontinue DMTs for a variety of reasons including cost, intolerable side effects, serious adverse events, (perceived or real) lack of efficacy, comorbid mental health disorders, and in our experience, the fact that taking a DMT reminds them of having MS [79–84]. Those with stable MS and minimal disability accrual over many years may in theory be good candidates for DMT discontinuation, though in a recent survey of 377 patients with MS, only 11.9% of respondents said they would consider DMT discontinuation if they had stable disease [18]. Patients who continue to progress despite DMTs tend to be the ones most interested in discontinuation. In the above survey, perceptions of DMT discontinuation appeared to be very influenced by the opinions of others, especially that of their neurologist. Regardless of how it happens, we have gained insights from the many patients who over the years have discontinued DMTs.

Observational cohort studies have identified cutoffs in middle-age after which DMT discontinuation is associated with a lower risk of disease activity. A small retrospective study of 22 DMT continuers and 13 DMT discontinuers over age 60 found that discontinuation did not influence clinical outcomes after a mean follow-up of 77.1 months [85]. In another small study, Yano et al. found that patients who discontinued after age 45 tended to have a stable course, while younger patients were more likely to experience clinical relapse or new MRI activity upon DMT discontinuation [86]. In an analysis of 132 DMT continuers and 366 discontinuers over age 50 followed for a median of 7 years, there was no difference in time to first relapse or time to disability progression between the groups, but discontinuation was associated with a higher risk of reaching an EDSS of 6 [87]. In a study of 100 SPMS discontinuers with a mean age of 47.2, annualized relapse rate remained stable at 1 and 3 years of follow up compared to on-treatment but 16 patients experienced an exacerbation and 19 had active lesions on MRI post-discontinuation [88]. A gadolinium-positive scan in the 3 years before discontinuation and EDSS < 6 were associated with relapse and/or MRI activity in this study. A study of the MSBase Registry found a similar time to first relapse between DMT continuers and propensity-score matched discontinuers, though time to disability progression was faster among discontinuers, driven by continued progression in those who had had progression prior to discontinuation

[89]. In a subsequent study from the same MSBase Registry involving 4842 patients with a median age of 35.9 years, the risk of relapse following DMT discontinuation was higher in younger patients, female patients, and those with moderate disability and a relapse within 1 year of discontinuation [90]. A Dutch study of 130 patients who stopped first-line DMTs (87.7% with relapsing–remitting MS, with average age of 45.3 at DMT discontinuation) found an exceptionally high rate of disease activity—60% [91]. In this study, higher age was associated with lower risk and severity of MRI activity and lower risk of relapse: patients older than 45 had over 3 times lower risk of MRI activity compared to younger patients.

Hua et al. performed regression analyses for various longitudinal outcomes in a retrospective cohort of 600 patients of at least 60 years of age (178 of whom discontinued treatment) and found that stopping DMT appeared to have minimal effect on these outcomes, with very few (19) discontinuers subsequently reinitiating therapy [92]. A French cohort study of 232 discontinuers with a mean age of 52.8 years found that risk of disease reactivation varied by DMT: in the year after discontinuation of a first-line agent, fingolimod, or natalizumab, 6%, 9%, and 43% of patients suffered relapses, respectively [93]. Time to relapse after discontinuation did not differ in this study according to whether the patient was younger or older than 55, though time to first MRI activity was faster in the younger group. Examining discontinuation of high-efficacy therapy in MS patients 50 years and older, a separate French cohort study including 168 discontinuers and 1452 propensity-matched continuers found an increased risk of inflammatory activity in discontinuers, which was both age- and DMT-dependent [94]. In particular, discontinuers of natalizumab and fingolimod experienced a significant increased risk of disease reactivation, even among patients with inactive SPMS, whereas discontinuers of rituximab and ocrelizumab did not. A systematic review of 22 articles and 2942 patients who had discontinued DMTs for longer than 12 months found that the risk of relapse became negligible (defined as less than 1% per year) at about 60 years of age, and after either 10 years of DMT exposure, or 8 years of disease stability [95]. Since the average 60-year-old with MS has had a disease duration of 30 to 40 years, these studies are less relevant for individuals with late-onset MS, who in general are less likely to be treated with DMTs despite the fact that they reach disability milestones at faster rates than those with adult-onset MS [96]. The discrepancy in discontinuation ages among all these retrospective studies likely reflects cultural differences and heterogeneity in real-world prescribing practices; they also highlight the fact that age alone is insufficient to determine when to recommend DMT discontinuation.

In addition to age and disease duration, the recent presence of disease activity has been shown to predict likelihood of recurrence upon DMT discontinuation. Researchers using the large Innsbruck MS Database found that age greater than 45 years at discontinuation, absence of relapses for at least 4 years on DMT prior to discontinuation, and absence of contrast-enhancing lesions predicted freedom from relapses after discontinuation [97]. A follow-up study from the same group leveraging generation and validation datasets of DMT discontinuers confirmed the importance of age, MRI activity at discontinuation, and duration of clinical stability as independent risk factors for disease reactivation, and a predictive model consisting of these variables was able to robustly identify patients at high (83–85%), moderate (36–38%) and low (7%) risk of disease reactivation within 5 years [98]. Serological measurements of biomarkers such as neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) may be helpful in predicting the likelihood of disease reactivation upon DMT cessation [99] though more research is needed in this area. More long-term observational discontinuation studies are also needed that include longer-acting agents such as anti-CD20 DMTs.

Until very recently, virtually all of the evidence for DMT discontinuation came from observational studies. The DISCOMS trial was the first multicenter randomized control trial (RCT) to test the hypothesis that DMT discontinuation was not inferior to treatment continuation in a typical population of middle-aged, stable MS patients [100]. Inclusion criteria specified at least 55 years of age, any MS subtype, no relapses in the preceding 5 years and no new MRI lesions in the prior 3 years. 6 (4.7%) of continuers and 16 (12.2%) of discontinuers had a relapse or new MRI activity during the trial. Given a non-inferiority margin of 8%, the null hypothesis was not rejected; discontinuation could not be declared non-inferior to continuation in this study. Nevertheless, the overall number of relapses in the trial was quite low—1 among continuers and 3 among discontinuers (no statistically significant difference on post-hoc analysis). Likewise, mean disability progression by EDSS or Symbol Digit Modality Test (SDMT, a cognitive test of psychomotor speed widely used in MS research) and number of individuals with confirmed disability progression did not differ between the two arms. At the start of the study, most participants felt "satisfied" or "very satisfied" (77% for continuers, 78% for discontinuers), and after 24 months, the proportion of satisfied participants remained stable among continuers while increasing to 91% among discontinuers ($p = 0.0086$). 15/22 (68.2%) of the events in DISCOMS consisted of 1–2 new brain lesions on MRI, with no association found between these and disability progression, raising a question about the clinical relevance of such radiographic changes.

The DOT-MS discontinuation RCT was halted prematurely in March 2023 after inflammatory activity (largely limited to MRI) emerged in 17.8% of the 45 participants who discontinued DMT, compared to none in those who

continued DMT [101]. Like DISCOMS, the DOT-MS trial randomly assigned half the participants, who were stable for at least 5 years, to stop their DMTs, while the other half continued them. Compared to DISCOMS, DOT-MS enrolled participants who were an average of 9 years younger. Those who developed disease reactivation in DOT-MS were on average 8 years younger than those who remained stable, corroborating the effect of age on risk of disease activity.

STOP-I-SEP (NCT03653273) is an ongoing French multicenter RCT for patients with secondary progressive MS over age 50, with moderate baseline disability (EDSS ≥ 3), estimated to end in January 2028. The primary endpoint for this trial is the percentage of patients experiencing confirmed disability progression at 2 years. We are narrowing in on the optimal age for DMT discontinuation and will continue to gain insights about age and other factors associated with discontinuation success from this and future studies.

### De-escalation and Rebound

As people age with MS, they may no longer experience any added benefit from high-efficacy DMTs but may still benefit from taking a low- or moderate-efficacy DMT. Analysis from our center found that younger patients tended to derive more benefit from highly effective DMTs (rituximab and natalizumab) compared to moderate efficacy oral agents (dimethyl fumarate and fingolimod), while patients older than 54.2 years benefitted equally with either approach [102] (in Weideman et al.'s meta-analysis, high-efficacy DMTs were superior to platform therapies only for those below 40.5 years [13]).

MS DMTs do not cause neurochemical changes like other medications or substances, such as opioids, whose discontinuation can unleash unopposed counter-regulatory forces and rapid withdrawal symptoms. Still, abrupt discontinuation of certain MS DMTs (or excessive gaps between DMTs) associated with lymphocyte trafficking or migration, such as natalizumab and the S1PR modulators, have been associated with the risk of rebound disease activity, even in those over age 50, though older patients may be at lower risk for disease reactivation [103–107] (see Fig. 1). De-escalation may not mitigate this risk. A prospective observational study of patients with MS transitioning from natalizumab to teriflunomide because of prior JC virus exposure found a low annualized relapse rate (ARR = 0.08) at 12 months, but 11 out of 55 (20%) had developed a new gadolinium-enhancing lesion [108]. Switching to interferon β from natalizumab resulted in the development of relapses in 22% and new T2 lesions in 75% of participants in a 1-year randomized pilot study [109]. The RESTORE trial, which randomly assigned patients who were stable on natalizumab for at least one year to continued natalizumab, placebo, or other therapies (interferon β-1a, glatiramer acetate, or methylprednisolone), reported 50/167 (30%) participants resuming natalizumab prior to week 28 because of disease activity [110]. The odds of developing higher numbers of gadolinium-positive lesions on MRI was 3.8 times greater (95% CI 1.71–8.56) in patients < 40 years compared to ≥ 40 years old in this trial [111]. Natalizumab Extended Interval Dosing (EID) has been implemented mainly to reduce the risk of PML, with encouraging efficacy data at an interval of 6 weeks [112–115]. EID of natalizumab does not seem to increase the rate of brain atrophy [116] or the levels of serum NfL [117] compared to standard interval dosing (SID). In the first phase of the NEXT-MS trial, which explored natalizumab dosing strategies based on trough levels, investigators found that personalized EID—in some cases out to 9 weeks—did not result in inferior clinical or radiographic outcomes compared to SID [118]. Whether such de-escalation strategies can lead to successful DMT discontinuation in older inactive MS patients is not yet known.

Most MS DMTs have only one or a limited number of approved dose strengths (lower doses available for initial titration, for example), but there have been some studies investigating off-label dosing regimens for some DMTs. Ghadiri et al. performed a systematic review of alternate day dosing of fingolimod, identifying 4 retrospective observational studies with a combined 296 on standard and 276 on alternate day dosing [119]. These studies differed in study populations, outcome measures, and methodologies. One study [120] found increased risk of relapses and MRI activity with every other day compared to standard dosing, but two others [121, 122] found similar rates of disease reactivation between the two regimens. The ASSESS trial, which separately compared daily doses of fingolimod 0.5mg or 0.25mg to glatiramer acetate (GA) 20mg, found that the higher fingolimod dose outperformed GA in annualized relapse rate, while the difference between the lower dose and GA was not statistically significant (The lower dose was statistically superior to GA on MRI measures of disease activity) [123]. GA exists in 20mg daily and 40mg three times weekly doses, though we have patients who prefer to take lower doses, for instance 40mg once or twice weekly; more evidence is needed to determine whether this kind of de-escalation strategy is valid. A monthly depot version of GA, not yet available as of this writing, may be attractive to older patients taking GA who are interested in limiting their injection burden, or even those taking other DMTs who want to de-escalate.

Using rituximab off-label for MS, neurologists initially adopted dosing practices from rheumatology and oncology, with 2 doses of 1000mg separated by 2 weeks, or 375mg weekly for 4 weeks, with repeated cycles every 6 months [124]. Our current practice is typically to administer single maintenance doses of 500mg once every 6 months, though

after March 2020, many patients experienced longer gaps between rituximab (and ocrelizumab) infusions due to the COVID-19 pandemic. In a single-center French study of all MS patients who started or continued rituximab after 2019, EID with a median gap of 17 months did not produce an appreciable difference in the annualized relapse rate, with 97% of patients experiencing radiographic stability in the EID period, despite partial or complete peripheral B cell reconstitution in the vast majority [125]. A Swedish retrospective study of 225 MS patients treated with rituximab who had discontinued treatment or reduced the dose to < 1000mg/year found no differences in annualized relapse rates, new or enlarging T2 lesions or contrast-enhancing lesions between full dose, reduced dose, and treatment discontinuation over a mean (SD) follow-up period of 6.5 (2.0) years [126]. Similarly, in a Swedish prospective, non-randomized cohort of 718 rituximab-treated MS patients stratified by interval (< 8, ≥ 8 to 12, ≥ 12 to 18, and ≥ 18 months), there was no relationship between time since last infusion and clinical or radiographic disease activity, despite variable B cell repopulation kinetics [127]. The ongoing RIDOSE-MS study (NCT03979456) is a Swedish non-inferiority RCT comparing rituximab 500 mg dosed every 6 months versus yearly, estimated to finish in June 2025.

Data from the ocrelizumab phase II extension study suggest durable efficacy 12–18 months after last infusion and an apparent decline in risk of infection toward the end of the treatment-free period [128]. A multicenter German study of ocrelizumab given at SID and EID (EID defined as ≥ 4-week delay in treatment) found high rates of freedom from relapse and MRI activity and low rates of disability progression with both dosing schemes [129]. Ocrelizumab EID resulted in repopulation of a higher percentage of transitional, naïve, and regulatory B cells, but not of memory B cells or plasmablasts, compared to SID in an immunological study of B cell subsets in which EID and SID had similarly very low rates of disease activity [130]. In Italian observational studies of relapsing and progressive MS patients on ocrelizumab, there was no difference disease activity or disability progression between SID and EID [131, 132]. Given the absence of rebound and their favorable pharmacodynamic properties, EID of intravenous anti-B cell DMTs is an attractive strategy to "wean off" DMTs, especially for natalizumab and S1PR modulators. At a minimum, de-escalation in any form can provide a psychological bridge for patients who are reluctant to quit DMTs "cold turkey."

## Conclusion

The observational and prospective controlled studies described above have defined several factors that should be considered when discussing potential permanent DMT discontinuation or de-escalation, including age, disease duration, recent clinical or radiographic activity or progression, current DMT, medical comorbidities, risks and costs with continued treatment, and patient preferences. Even in the best possible scenario, clinicians and patients approaching this issue are often confronted with more questions than answers. What is the risk of disease activity when the DMT is reduced or eliminated? How much time will have to pass off therapy before we are "in the clear?" What symptom or event would support treatment re-initiation? Is any amount of disease activity, however small, acceptable? And relatedly, if small lesions appear on follow up brain MRIs of older discontinuers, how confident can we be that they are MS lesions and not microvascular changes? Given the greater benefits on relapses and MRI activity than on disability progression generally with MS DMTs, and the especially limited impact of presently available DMTs on progression in older patients, it is worth considering the inflammatory activity and PIRA axes separately when evaluating whether or not treatment discontinuation has been "successful." The fact that someone experiences PIRA after DMT cessation does not necessarily mean that they would not have had the same progression had the DMT been continued.

Given the information available to date, we would conclude it is reasonable to begin having DMT de-escalation and discontinuation discussions with patients of any MS subtype fulfilling the following criteria: 1) Age 50 to 55 years; 2) Minimum time from last relapse or MRI change of 5 years; and 3) Disease duration of at least 15 years. Conversations may need to be continued over several visits. A stepwise de-escalation plan can be offered to those wishing to reduce DMT risk who are fearful of disease recurrence with abrupt discontinuation, though more research is needed to refine de-escalation strategies. We recommend that DMT discontinuers continue to be followed with periodic examinations and neuroimaging to evaluate for stability, for example, obtaining a brain MRI at the time of discontinuation and annually for 2 years and if stable as needed thereafter, and clinical follow up every 6 months for 2 years and if stable annually thereafter. Clinical or radiographic worsening should prompt reconsideration of the discontinuation decision, although data from DISCOMS indicate that one or two new lesions on brain MRI are not associated with significant risk of disability progression [105]. Fears of disease reactivation following DMT discontinuation should not be quickly dismissed regardless of a patient's age or disease duration, since older patients may still have *some* (albeit low) risk of disease reactivation. Even a predicted 99% chance of success might be met with skepticism by someone currently content with their DMT. It is important to emphasize to the patient that discontinuation does not mean abandonment of care.

In general, there remains relatively limited research in MS patients over age 55 on the use of and de-escalation/

discontinuation from DMTs, especially involving long-term follow up. Future studies will be needed to pinpoint an individual's optimal moment for permanent DMT discontinuation, to identify biomarkers (fluid, imaging) with stronger predictive power, to refine prognostic algorithms for de-escalation and discontinuation, and to gauge the benefits of DMT resumption in discontinuers following new MRI findings or clinical symptoms. Introduction of novel interventions such as CAR-T therapies or MS vaccines that tolerize the immune system in a more durable way may further reshape the concepts of DMT de-escalation and discontinuation. In a future that includes neuroprotective, remyelinating, and regenerative treatments in addition to standard immunotherapies, paradigms of DMT de-escalation and discontinuation will evolve: one might imagine an overlapping treatment framework prioritizing immunotherapies for the first several years, remyelinating/repair agents as needed (e.g. following a relapse) or until desired functional outcomes are achieved, and neuroprotective agents throughout the course.

## Case

A 60-year-old woman with MS presented to our clinic to establish care. She was originally diagnosed with MS 36 years ago after an episode of diplopia and has had progressive decline in her gait beginning about 15 years ago, consistent with a secondary progressive phenotype. She began walking with a cane 10 years ago and more recently has become more reliant on a walker. 3.5 years ago after her partner's death, her family became aware of how dependent she had become. Chronic symptoms included mild paraparesis, gait ataxia, urinary incontinence, and cognitive impairment. She has been receiving natalizumab infusions for the past 5 years. MRIs of the brain during this time have shown stable moderate burden of demyelinating lesions in the juxtacortical, deep, periventricular, and infratentorial white matter, with severe global volume loss and no gadolinium-enhancing lesions. 2 years ago, she was hospitalized for generalized seizures, now controlled with levetiracetam. At initial evaluation, her Expanded Disability Status Scale was 6.5. We agreed to discontinue natalizumab. At a return visit 7 months later, she reported worsened balance and falls. New noncontrast brain MRI revealed a new lesion in the left pons and middle cerebellar peduncle (see Fig. 1). Natalizumab was resumed without further relapses or MRI changes in the following 5 years, though she continued to experience slow decline, increasingly needing to use a wheelchair.

*Lesson*: Natalizumab discontinuation should be approached cautiously, even in older progressive patients, given the risk of disease reactivation. Extended interval dosing or switching to an anti-CD20 immunotherapy should be considered.

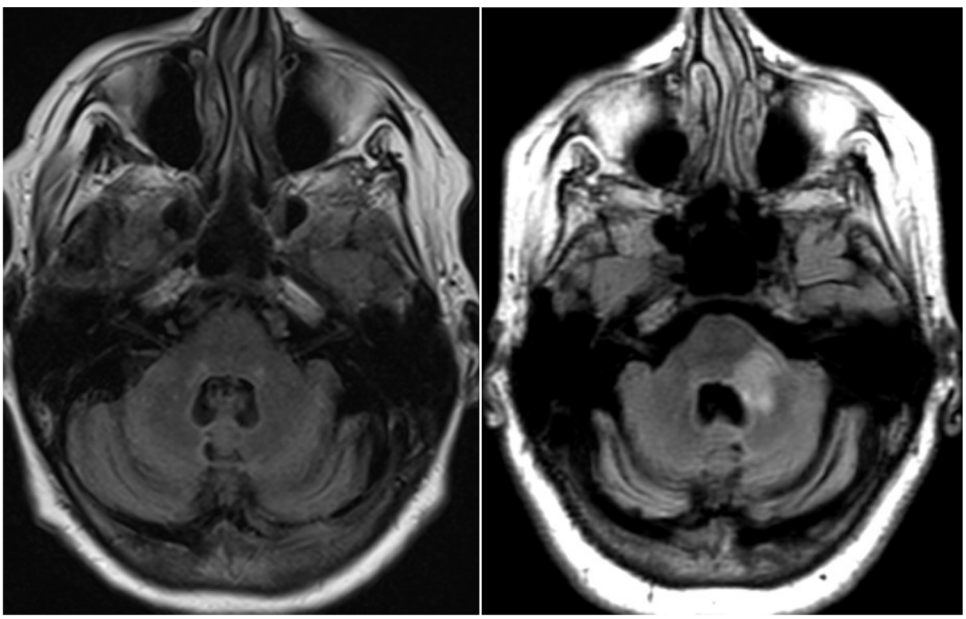


**Fig. 1** Baseline brain MRI. MRI brain 7 months later

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– Comprehensive overview of changes associated with aging in MS

**Author contributions** R.G. and J.C. wrote the main manuscript text, prepared the figure and the table, and jointly reviewed the manuscript.

## Declarations

**Competing interests** The authors declare no competing interests.

**Conflicts of interest/ Competing interests** RHG has no relevant financial or non-financial interests to disclose. JC reports personal fees from *Annals of Neurology*, personal fees from Rocky Mountain Multiple Sclerosis Center, grants from NIH/ Immune Tolerance Network, grants from EMD Serono, personal fees from Clene Biosciences, grants and personal fees from Bristol Myers Squib, and grants from National Multiple Sclerosis Society and Patient-Centered Outcomes Research Institute.

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