

2 **De-escalating and discontinuing disease-modifying therapies**  
3 **in multiple sclerosis**

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16 **Abstract**

17 The development of disease-modifying therapies (DMTs) for the treatment of multiple sclerosis  
18 (MS) has been highly successful in recent decades. It is now widely accepted that early initiation  
19 of DMTs after disease onset is associated with a better long-term prognosis. However, the question  
20 of when and how to de-escalate or discontinue DMTs remains open and critical. This topic was  
21 discussed during an international focused workshop organized by the European Committee for  
22 Treatment and Research in Multiple Sclerosis (ECTRIMS) in 2023. The aim was to review the  
23 current evidence on the rationale for, but also the potential pitfalls of, treatment de-escalation in  
24 MS. Several clinical scenarios emerged, mainly driven by a change in the benefit-risk ratio of  
25 DMTs over the course of the disease and with aging. The workshop also addressed the issue of de-

1 escalation by the type of DMT used and in specific situations including pregnancy and paediatric  
2 onset MS. Finally, we provide practical guidelines for selecting appropriate patients, defining de-  
3 escalation and monitoring modalities, and outline unmet needs in this field.

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14 pregnancy

## 16 Introduction

17 Disease-modifying therapies (DMTs) for the treatment of multiple sclerosis (MS) have developed  
18 considerably over the last 30 years; their goal has gradually shifted from reducing relapse rates to  
19 achieving complete control of the peripherally-mediated inflammatory component of the disease.<sup>1,2</sup>

20 Therapeutic algorithms are continuously being refined, and it is now broadly accepted that greater  
21 benefits of DMTs, in terms of relapse prevention and delayed progression, can be achieved if an  
22 appropriately effective treatment is initiated early after disease onset.<sup>3,4</sup> The selection of DMTs is  
23 guided by a benefit-risk assessment, fed by the debate between escalation and early high-efficacy  
24 therapeutic regimens.<sup>5,6</sup> Most of MS DMTs are given continuously. These maintenance therapies  
25 include molecules known as “platform therapies”: interferon- $\beta$  (IFN- $\beta$ ), glatiramer acetate (GA),  
26 teriflunomide (TRF), dimethyl fumarate (DMF)/ diroximel fumarate (DRF), as well as “high-  
27 efficacy therapies” (HETs), including anti-CD20 antibodies and drugs targeting the traffic of

1 immune cells such as natalizumab (NTZ) and sphingosine-1-phosphate receptor (S1PR)  
2 modulators. The alternative to these maintenance therapies is to administer HETs either once or in  
3 a sequential manner which may allow for higher adherence to treatment and lower risks of long-  
4 term cumulative side effects associated with chronic immunosuppression. This category, also  
5 known as immune reconstitution therapies (IRTs), includes the oral formulation cladribine (CLA),  
6 the anti-CD52 antibody alemtuzumab (ALZ), mitoxantrone (MTX) and autologous haematopoietic  
7 stem cell transplantation (AHSCT).<sup>7-10</sup>

8 Beyond the optimal selection of DMTs, there is a need for de-escalation algorithms that justify  
9 regular reassessment of treatment plans with the aim of reducing treatment intensity or even  
10 discontinuing treatment if the benefit-risk ratio becomes less favourable.<sup>11</sup> In this context,  
11 understanding the principles, challenges, and evolving evidence surrounding de-escalation  
12 strategies is paramount to optimising long-term outcomes, mitigating risks, and improving the  
13 quality of life for people with MS (pwMS). To date, however, there is no consensus on the  
14 strategies of de-escalation or discontinuation, while a similar concept has been discussed more  
15 extensively in other fields, such as rheumatology or oncology.<sup>12,13</sup> To fill this gap, the 2023 Annual  
16 Focused Workshop organised by the European Committee for Treatment and Research in Multiple  
17 Sclerosis (ECTRIMS) brought together a panel of international experts to review and discuss the  
18 current evidence on de-escalating DMTs in MS. The aim of this workshop was to provide evidence-  
19 based practical recommendations for the management and monitoring of de-escalating DMTs.

20

## 21 **The scope of de-escalation strategies**

22 De-escalation usually refers to a switch from one DMT to a less potent one. For some treatments,  
23 de-escalation strategies may also include decreasing the dose or extending the dosing interval.  
24 Discontinuation, which refers to a permanent or temporary (e.g. around pregnancy) DMT  
25 withdrawal, shares patient selection and monitoring challenges with de-escalation. This is why we  
26 propose including discontinuation in de-escalation strategies. Unscheduled discontinuation due to  
27 intolerability or serious adverse effects does not belong strictly to de-escalation strategies and will  
28 not be addressed here. De-escalation strategies apply to all DMTs. For IRTs, de-escalation can  
29 even be considered as part of their mechanism of action, as these are expected to induce prolonged  
30 remission without additional DMT or with less potent maintenance therapy.

1

## 2 **The rationale for de-escalation**

3 A change in the benefit-risk balance in a given patient represents the main reason for modifying or  
4 discontinuing a DMT (Fig.1). This may be related to a decrease in expected effectiveness and/or  
5 an increase in treatment or host-related risks (Fig. 2). Age-associated changes in the immune  
6 system play a crucial role in both cases.

7

## 8 **Immunosenescence, inflammaging and their relevance to MS** 9 **pathogenesis**

10 Immunosenescence (ISe) refers to the gradual decline in immune function while inflammaging  
11 (IA) corresponds to chronic low-grade inflammation, both occurring with aging.<sup>14</sup> ISe is  
12 characterised by quantitative and/or qualitative changes of T-cells, B-cells and subsequently  
13 antibodies.<sup>15,16</sup> To a lesser extent, ISe affects the innate immunity, consisting of monocytes and  
14 macrophages, microglia, dendritic cells, neutrophils, and natural killer cells.<sup>17</sup> These cells show  
15 reduced migration, phagocytic and cytotoxic abilities. All these processes may contribute to an  
16 increased incidence of cancer and infection, as well as a reduced response to vaccination in the  
17 elderly.<sup>14</sup> IA is thought to be caused by the accumulation of senescent cells, chronic viral infections  
18 and dysregulation of the immune system.<sup>18</sup> CNS macrophages/microglia tend to differentiate into  
19 a pro-inflammatory phenotype that affects neighbouring cells and contributes to impaired tissue  
20 repair.

21 People with MS (pwMS) have traditionally been classified as having relapsing-remitting (RR) or  
22 progressive (either secondary SP or primary PP) MS. Increasing evidence suggests that MS should  
23 be better viewed as a continuum, with varying contributions of inflammatory and  
24 neurodegenerative processes between individuals and over time.<sup>19,20</sup> Relapses are associated with  
25 focal demyelinating lesions related to the infiltration of peripheral immune cells (mainly T and B  
26 cells) across the blood-brain barrier (BBB). During the progressive phase of MS, peripheral  
27 immune involvement is secondary to diffuse and compartmentalised CNS inflammation dominated



1 by microglial activation and meningeal infiltration.<sup>21</sup> Both processes correlate with diffuse  
2 neuroaxonal loss, which is thought to be the main substrate of progressive disability in MS.<sup>22,23</sup>  
3 Thus, pwMS may acquire disability either through relapse-associated worsening (RAW) or  
4 progression independent of relapse activity (PIRA).<sup>24</sup> Recently, PIRA has been shown to start early  
5 in the disease process, even in RRMS, and to become the main driver of disability accumulation  
6 with increasing age and disease duration.<sup>24,25</sup> Age has long been suspected to play a role in the  
7 pathogenesis of progression, as the median age at onset of the progressive phase was similar in SP  
8 and PP patients, between 40 and 45 years.<sup>26,27</sup>  
9 Therefore, ISe and IA may play a role both in the decrease of focal inflammatory activity and the  
10 progressive neurodegeneration observed with increasing age in MS and in the variation of efficacy  
11 and risks of DMTs (Fig 1).<sup>28</sup>  
12

### 13 **Efficacy issues**

14 Several studies have documented a continuous decline in focal inflammatory activity with disease  
15 duration. In a largely untreated cohort of 2,477 patients, the relapse rate was found to be related to  
16 both age and disease duration, decreasing by an average of 17% every 5 years.<sup>29</sup> Likewise, data  
17 from four randomised controlled trials (RCTs) showed an inverse correlation between age and the  
18 occurrence of contrast-enhancing lesions (CELs), a biomarker of focal inflammatory activity.<sup>30</sup>

19 As all approved DMTs primarily target the peripheral immune system, their effect on the course of  
20 MS in later stages may be limited. Evidence to test this hypothesis is scarce, as almost all phase 3  
21 clinical trials have excluded patients over the age of 55. This is in contrast with the current peak  
22 age of MS prevalence estimated between 55 to 64 years.<sup>31</sup> Longer life expectancy improved  
23 medical care and potentially increased late-onset MS (LOMS, onset 50 years or older) incidence  
24 contribute to this observation.<sup>32</sup> A meta-analysis with linear regression model of 38 clinical trials  
25 analysing over 28,000 patients with RR, SP or PPMS showed a loss of efficacy of DMTs on  
26 disability progression after approximately age 53. In this study, the difference between high-  
27 efficacy and low- to moderate- efficacy drugs disappeared in patients older than 40.5 years.  
28 However, this meta-analysis may be underpowered for the oldest patients, who are excluded from  
29 most RCTs. In contrast, a multicentre study using data from the MS Base registry and propensity

1 score matching showed that ocrelizumab (OCR) still significantly reduced the annualized relapse  
2 rate (ARR) by a ratio of 0.15 compared with IFN- $\beta$ /GA in pwMS over 60 years of age (n=248 and  
3 427 respectively).<sup>33</sup>

4 In RRMS, early initiation of DMTs has been shown to delay conversion to the SP phase, with  
5 superiority of HETs.<sup>34</sup> However, the effectiveness of DMTs, including HETs, in slowing  
6 progression once started is uncertain. Although NTZ has shown potent anti-inflammatory effect in  
7 RRMS, it did not reduce progression on the primary composite disability endpoint in the phase 3  
8 ASCEND trial.<sup>35</sup> Siponimod has demonstrated efficacy in SPMS but the difference versus placebo  
9 was not statistically significant in the subgroup of patients without superimposed relapses in the  
10 two years before enrolment.<sup>36</sup> To date, the only approved therapy that has shown efficacy in PPMS  
11 is OCR but with a moderate effect size and a greater impact in patients with active disease, mirrored  
12 by CELs at inclusion.<sup>37</sup> Furthermore, the study by Foong et al.<sup>33</sup> failed to show a differential effect  
13 between OCR and IFN- $\beta$ /GA on confirmed disability progression at 3.5 years in pwMS over 60  
14 years of age.

15

## 16 **Safety issues**

17 As all DMTs impact the immune system, the risk of infections is the most common safety concern  
18 (Fig.2). DMTs are considered immunosuppressive when they cause lymphocyte depletion,  
19 hypogammaglobulinemia or impaired cellular trafficking. Alemtuzumab, AHSCT and intravenous  
20 anti-CD20 agents have been associated with an increased frequency of serious infections (i.e.  
21 requiring hospitalization) compared to other DMTs.<sup>38,39</sup> The risk of infection with RTX was  
22 significantly correlated with age, level of disability, obesity, lymphopenia,  
23 hypogammaglobulinemia and treatment duration.<sup>38,40-42</sup> These factors are not independent of each  
24 other, as age is associated with reduced lymphocyte and immunoglobulin production and disability  
25 accrual. Hypogammaglobulinemia is also related to the cumulative dose of intravenous B-cell  
26 depleting agents, RTX and OCR.<sup>43</sup> On the other hand, higher cumulative doses of RTX increase  
27 the risk of infection even in the case of normal IgG levels.<sup>40</sup> Overall, the level of disability emerged  
28 as the most important risk factor for serious infections on RTX, with an odds ratio around 9 for  
29 wheelchair-bound versus fully ambulatory pwMS.<sup>40,41</sup> These findings are likely to be relevant to

1 other anti-CD20 drugs, although long term follow-up of the pivotal OCR studies does not seem to  
2 support a significantly higher risk of infections.<sup>43</sup>

3 In addition, aging is associated with an increased risk of opportunistic infections. Progressive  
4 multifocal leukoencephalopathy (PML) due to JC virus infection is more frequent in pwMS older  
5 than 50 years whether on NTZ, FTY or DMF.<sup>44–46</sup> A duration of NTZ treatment of more than 2  
6 years is an established risk factor for PML.<sup>47</sup> Other infectious complications such as FTY-  
7 associated cryptococcal meningitis are also related to aging and duration of treatment.<sup>48</sup> Older age  
8 is associated with a higher risk of DMF-induced lymphopenia and a longer time to lymphocyte  
9 repopulation after cessation.<sup>49</sup> Moreover, vaccine responsiveness, including COVID-19  
10 vaccination, is attenuated with certain DMTs such as S1PR modulators and B cell-depleting  
11 therapies (Fig.2).<sup>50,51</sup> As previously mentioned, ISe may also contribute to reduced vaccine  
12 efficacy.

13 Given their action on the immune system, there has always been a concern about cancer risk with  
14 long-term use of DMTs (Fig. 2). Although some data are contradictory, the overall incidence of  
15 cancer in pwMS seems comparable to that of the general population, which means it increases with  
16 age.<sup>52</sup> Previously used off-label immunosuppressants have been associated with a dose-dependent  
17 increase in cancer risk, such as azathioprine after 10 years of continuous exposure.<sup>53</sup> Medium term  
18 exposure to NTZ and RTX does not increase cancer risk.<sup>54</sup> FTY is associated with a higher  
19 incidence of skin cancer.<sup>55</sup> The initially suspected increased risk of breast cancer with OCR was  
20 not confirmed in an analysis of 11 clinical trials and post-marketing data, or with RTX use in  
21 MS.<sup>43,54</sup> However, a meta-analysis with meta-regression of 45 RCTs suggested an increased risk  
22 of neoplasia with cell-depleting monoclonal antibodies (OCR and ALZ) above an average age of  
23 45 years in comparison with other DMTs.<sup>56</sup>

24 Another concern is the long-term risk of sequential drug use with different mechanisms of action.  
25 Data assessing the cumulative effects of successive DMTs are scarce, although a recent study found  
26 no significant effect of previous DMT exposure on the risk of infection with RTX.<sup>42</sup>

27 Finally, with age, there is a greater propensity to accumulate comorbidities that may increase both  
28 the risk of interactions between MS DMTs and treatments for emerging comorbidities and the  
29 specific risks of DMTs.<sup>28,57</sup>

30

## 1 **Patients' willingness**

2 After several years of continuous treatment, some pwMS experience weariness resulting in  
3 compliance issues. It is difficult to assess whether long-term DMTs have a positive or negative  
4 impact on quality of life. A retrospective observational study of 600 pwMS aged 60 and over  
5 demonstrated significant difference over time, with continuers having lower quality of life scores  
6 than discontinuers.<sup>58</sup> However, it is noteworthy that most discontinuations concerned IFN- $\beta$  and  
7 GA, both associated with frequent injection-related side effects.<sup>59</sup>

## 8 9 **Economic and regulatory considerations**

10 DMTs are the main drivers of the substantial economic burden of MS.<sup>60</sup> They account for 65% of  
11 excess costs in a recent retrospective-matched cohort study of 17,000 pwMS.<sup>61</sup> Whether the cost  
12 of DMTs is counterbalanced by the reduction of other direct (e.g. hospitalizations) and indirect  
13 (e.g. work incapacity) expenses is still being debated.<sup>62</sup> In any case, the question of cost-  
14 effectiveness should be regularly addressed during the MS course. Furthermore, regulatory  
15 indications, reimbursement, and health insurance coverage issues, which vary by country, may  
16 affect the decision to stop or continue certain DMTs.

## 17 18 **The potential risks of treatment de-escalation in MS**

### 19 20 **Risk of disease reactivation**

21 Acute inflammatory activity in MS is defined clinically by the occurrence of clinical relapse(s) or  
22 radiologically by the occurrence of CELs or new or enlarging T2 lesion(s).<sup>63</sup> Table 1 shows the  
23 main recent studies evaluating the risk of reactivation after DMT discontinuation, helping to profile  
24 patients with greater risk.<sup>58,64-74</sup> Until very recently, all available studies were retrospective and  
25 observational. Their methodology was heterogeneous, but most suggested that the risk of return of

1 disease activity is lower in older patients without recent relapse or MRI activity. The cut-offs for  
2 age and for the period without clinical or radiological activity ranged from 45 to 60 years, and from  
3 2 to 5 years, respectively. There were conflicting data on the impact of Expanded Disability Status  
4 Scale (EDSS) score on the risk of reactivation. A recent meta-regression analysis based on 22  
5 articles, most of which are listed in Table 1, representing 2942 patients, showed that the risk of  
6 relapse was less than 1% per year at about age 60, after either 10 years of DMT exposure or 8 years  
7 of disease stability.<sup>58,64–70</sup> While these observational studies mostly assessed disease activity after  
8 discontinuation of platform therapies, a recent retrospective propensity score-based study from the  
9 French OFSEP database examined this risk in RRMS and SPMS patients older than 50 years with  
10 no evidence of focal inflammatory activity for 2 years or more who discontinued HET.<sup>64</sup> The  
11 probability of a first relapse after 1-year follow-up was greater (15.3%) in the entire discontinuation  
12 group than that observed in the continuation group (3%). However, the increased risk of relapse  
13 only concerns stopping anti-cell trafficking therapies (NTZ and FTY) but not B cell depleting  
14 therapies (see below).

15 In the DISCOMS RCT, which was a non-inferiority study, 259 patients with any phenotype of MS,  
16 aged 55 and over, with no relapse in the past 5 years or new MRI lesion in the past 3 years were  
17 randomised to either continue or discontinue DMT.<sup>66</sup> Although no significantly higher risk of  
18 relapse was observed, the study failed to demonstrate the non-inferiority of treatment  
19 discontinuation versus continuation on the primary endpoint, which combined the percentage of  
20 patients with relapse and radiological activity. Moreover, the proportion of HETs in this study was  
21 very low, probably restricting the generalisability of these results to discontinuation of platform  
22 DMTs.

23 The DOT-MS trial (NCT04260711) was a multicentre randomised controlled non-inferiority trial  
24 that included people with relapse onset MS aged over 18 years without any relapse or MRI activity  
25 in the previous 5 years while on platform DMTs. This trial was prematurely discontinued because  
26 of excessive disease activity in the discontinuation group. During a median follow-up of 12 months,  
27 6/45 patients in the discontinuation group experienced disease activity including two relapses vs  
28 0/44 participants in the continuation group. Of note, the mean age at enrolment was 53.5 years (i.e.  
29 almost 10 years younger than in the DISCOMS trial) while the mean age of the six patients who  
30 relapsed was 48.7 years.

1 Two other RCTs are still ongoing. STOP-I-SEP (NCT03653273) studies the effect of DMT  
2 discontinuation (except anti-cell trafficking agents) in SPMS patients older than 50 years with  
3 clinically and radiologically stable disease for 3 years. The primary endpoint of this study is EDSS  
4 progression at 2 years, but the occurrence of relapse and MRI activity will also be assessed. TWINS  
5 (EUCT 2024-513475-41-00) will investigate DMT cessation in RRMS patients, aged over 55,  
6 clinically and radiologically stable for 5 years.

7

## 8 **Risk of rebound**

9 To date, there is no consensus definition of the rebound phenomenon. However, this term  
10 commonly refers to an increase in disease activity compared with the pretreatment level, occurring  
11 after DMT discontinuation in terms of ARR and/or MRI activity.<sup>75</sup> Some authors have proposed  
12 additional criteria such as: one or more severe relapse associated with a sustained one-step EDSS  
13 increase, three or more new T2 lesions and/or gadolinium-enhanced lesions on MRI, and one or  
14 more new tumour-like lesion.<sup>76</sup> Rebound cases have been described after discontinuation of anti-  
15 lymphocyte trafficking DMTs, i.e. NTZ and FTY.<sup>75,77,78</sup> Rapid re-entry of lymphocytes into the  
16 CNS is thought to be the main mechanism. The risk of rebound after other S1PR modulator  
17 cessation (ozanimod, ponesimod, siponimod) is less certain. To our knowledge, only one case of  
18 substantial disease exacerbation after siponimod withdrawal has been reported to date.<sup>79</sup> In  
19 contrast, none of the other DMTs have been associated with a rebound phenomenon after  
20 discontinuation,<sup>69</sup> including anti-CD20 therapies.<sup>80</sup>

21 The meta-analysis by Prosperini et al.<sup>75</sup> included 35 studies reporting the effects of NTZ withdrawal  
22 on MS activity. Clinical relapses were observed in 9–80% of patients and peaked between 4 to 7  
23 months after NTZ discontinuation, whereas MRI activity was observed in 7–87% of patients from  
24 6 weeks after stopping. In this review, only eight studies looked specifically at the risk of rebound,  
25 which was found between 8 and 22%. Mustonen et al.<sup>81</sup> reported that 8 out of 89 patients (9%)  
26 showed signs of rebound with a median time to onset of 3 [1–4] months after stopping NTZ. Several  
27 risk factors for disease reactivation and/or rebound after NTZ withdrawal have been identified:  
28 younger age, high disease activity before NTZ initiation, shorter treatment duration, and longer  
29 washout (more than 2 months) before DMT re-introduction.<sup>69,75,81</sup>

1 Reported rebound rates after FTY discontinuation are quite similar to those reported for NTZ,  
2 ranging from about 10% to 33% across retrospective studies.<sup>77,82–85</sup> The risk factors for rebound  
3 are also more or less the same as for NTZ: younger age,<sup>83,86</sup> high disease activity before treatment  
4 initiation and longer washout.<sup>69</sup>

## 6 **Risk of accelerated progression**

7 Although most of studies have failed to demonstrate a significant effect of DMTs on relapse-  
8 independent progression, some suggested an acceleration of progression after DMT cessation.  
9 Among 161 patients with RRMS or SPMS (average age of 50.6 years) who were considered as  
10 stable before DMT discontinuation (e.g. no change in EDSS score or an increase of <1.0 if EDSS  
11 <6.0 or <0.5 if EDSS  $\geq$ 6.0), about one third experienced disability progression after DMT  
12 discontinuation.<sup>68</sup> One major limitation of this study was the lack of information regarding the  
13 reason for DMT stopping. It may have resulted from a lack of efficacy perceived by the patient,  
14 due to insidious progression undetected by EDSS. In addition, the lack of matched patients  
15 remaining on DMT does not rule out natural disease progression unrelated to DMT discontinuation.  
16 However, a MS Base propensity score-matched study found similar results.<sup>87</sup> In a population of  
17 pwMS who were relapse-free for at least 5 years on IFN- $\beta$  or GA, time to first relapse was similar  
18 but time to confirmed disability progression was significantly shorter among stoppers than stayers  
19 but in a limited number of patients.

20 On the other hand, an observational study of 100 SPMS patients found no difference in the rate of  
21 disability progression in the 3 years after stopping treatment compared to the 3 years before.<sup>88</sup> Of  
22 note, all patients were treated with IFN- $\beta$  or GA. It cannot be excluded that progression after  
23 discontinuation differs between treatments, as, for example, OCR appears to be superior to IFN- $\beta$   
24 and OFA to TRF in preventing PIRA in RCTs conducted in RRMS patients.<sup>89,90</sup> The STOP-I-SEP  
25 trial is expected to provide further answers to this important question.

26

## 1 **Risk of poor recovery of relapse with aging**

2 Relapses are very infrequent among pwMS aged  $\geq 60$  years.<sup>29</sup> However, older age was significantly  
3 associated with worse recovery after a relapse, as demonstrated by two recent analyses covering  
4 more than 300 relapses in each study.<sup>24,91,92</sup> The age-related decline in relapse recovery may be due  
5 to a reduction in remyelination capacity due to impaired recruitment and differentiation of  
6 oligodendrocyte precursors.<sup>93</sup> As previously seen, ISe and IA are involved in the decreased repair  
7 capacity.<sup>28</sup> Neurodegenerative processes associated with aging could also explain a higher  
8 vulnerability of axons to demyelination as well as a lack of compensatory reserve.

## 10 **Patient concerns**

11 "Will I have to take my treatment for the rest of my life?" is one of the most common questions  
12 asked by patients newly diagnosed with MS who have been prescribed their first DMT. However,  
13 many years later, discontinuation of DMT can cause anxiety in pwMS. In the study of Mc Ginley  
14 et al.,<sup>94</sup> a questionnaire was sent to 1,000 pwMS aged 45 years and older who had been on the same  
15 DMT for at least 5 years. Of the 377 patients who responded, only 12% said they would consider  
16 stopping DMTs if their disease was stable; 22% were unsure and 66% were unlikely.

## 18 **Main de-escalation scenarios in adult patients with MS**

19 The above section has outlined the rationale for DMT de-escalation in MS, leading to several  
20 situations in which this question should be addressed in clinic.

21 The first scenario is that of aging pwRRMS and stable disease (Fig. 3).<sup>11</sup> Cut-off values for age  
22 and duration of stable disease have not been fully defined, but the risk of disease reactivation  
23 appears to be low in patients aged between 55 and 60 years without clinical or radiological evidence  
24 of activity for at least 5 years. This is consistent with the proposed criteria for so-called burn-out  
25 MS, i.e. elderly RRMS patients ( $\geq 55$  years) with prolonged absence of focal inflammation ( $\geq 5$   
26 years) and without secondary progression.<sup>71</sup> However, these guidelines should be considered on an  
27 individual basis, taking into account additional factors such as MS activity prior to treatment and



1 type of DMT used. The age cut-off must also be weighted by the disease duration, which is  
2 correlated with the risk of relapse.<sup>29</sup> This is particularly relevant as the incidence of LOMS appears  
3 to be increasing.<sup>32</sup> On the other hand, lowering the age limit for certain forms of MS considered  
4 "benign" may be questionable, as the term "benign" MS is controversial. Historically, benign MS  
5 has been defined by an EDSS<3 at 10 to 15 years of disease duration, theoretically without DMT,  
6 and is therefore difficult to apply today when most pwMS are treated from their first relapse. In  
7 addition, this definition fails to capture less visible symptoms such as fatigue, pain or cognitive  
8 impairment.<sup>95</sup>

9 The second scenario includes older pwMS with pure progression.<sup>11</sup> The recommendations of the  
10 Canadian MS Working Group proposed to consider discontinuing treatment in inactive pwMS with  
11 progression, especially if they are older (>60 years) with a prolonged period (>5 years) without  
12 new inflammatory disease activity.<sup>96</sup> According to the practice guideline recommendations of the  
13 American Academy of Neurology, clinicians may advise discontinuation of DMT in people with  
14 SPMS who do not have ongoing relapses or CELs and have not been ambulatory (EDSS≥7) for at  
15 least 2 years.<sup>97</sup>

16 In addition to these two scenarios, the decision to de-escalate may be considered in younger patients  
17 when individual factors may have a negative impact on the benefit-risk balance (Fig.2 and 3).<sup>98</sup>  
18 These include but are not restricted to advanced disability (EDSS≥7), the occurrence of recurrent  
19 infections or a serious infection, a progressive decrease in IgG levels under anti-CD20 treatment,  
20 the presence of a comorbidity, a diagnosis of cancer, etc.

21  
22 A third situation is that of temporary de-escalation related to a planned or ongoing pregnancy (Fig.  
23 4). As first shown by the PRIMIS study and subsequently confirmed by many other studies, the  
24 relapse rate decreases during pregnancy.<sup>99</sup> Given this finding and the restrictive nature of drug  
25 approvals, some clinicians tend to systematically discontinue DMT prior to conception. Others do  
26 not initiate DMT if there is a short-term pregnancy plan. However, the protective effect of  
27 pregnancy is not always sufficient to prevent a disease reactivation, or even a rebound, particularly  
28 in women who stop anti-cell trafficking DMTs.<sup>100-104</sup> In recent years, increased knowledge and  
29 therapeutic options have made it possible to control the disease before, during and after pregnancy  
30 in most cases. For this purpose, treatment decisions need to be individualised, shared with the

1 patients and their partners, and anticipated as far as possible.<sup>70,101</sup> Importantly, any DMT choice  
2 for a woman of childbearing age must take into account her family planning.

3

## 4 **De-escalating strategies depending on DMT types**

5 De-escalation modalities vary from one DMT to another. Table 2 and Figure 3 summarise the  
6 current state of knowledge and suggest some practical guidelines for de-escalation strategies based  
7 on the type of DMT.

8

## 9 **Platform therapies**

10 If the patient has been stable while on a platform therapy including IFN- $\beta$ , GA, TRF and  
11 DMF/DRF, it is not logical to consider switching to a treatment of similar efficacy. Discontinuing  
12 DMT is therefore the main option. In the DISCOMS trial and most of the observational studies  
13 cited in the Table 1, most patients (73-100%) were treated with IFN- $\beta$  or GA.<sup>66,70,71,73</sup> The risk of  
14 relapse has been shown to be low and mainly related to age and time since last observed MS  
15 activity. No risk of rebound of disease activity has been observed. This was confirmed in a large  
16 retrospective cohort study from MS Base and OFSEP registries, whether for IFN- $\beta$  (n=8,933  
17 patients), GA (n=2,891), TRF (n=389) or DMF (n=553).<sup>69</sup>

18

## 19 **Fingolimod (and by extension other S1PR modulators)**

20 Given the significant risk of relapse or even rebound, abrupt discontinuation of a S1PR modulator  
21 should be avoided. As a result, patients treated with FTY are poorly represented in the observational  
22 discontinuation studies and are even excluded from the STOP-I-SEP trial (Table 1). In the study of  
23 Jouvenot et al.,<sup>64</sup> patients over 50 who stopped FTY without switching to another treatment, after  
24 at least 2 years without disease activity, had a hazard ratio (HR) of 4.5 (95% CI 1.3-15.5, p=0.018)  
25 for experiencing a relapse in the year after discontinuation compared with the continuation group  
26 (n=51 in each group).

1 Other available data mostly come from studies in which FTY was discontinued due to lack of  
2 efficacy or intolerance and cannot be fully extrapolated to the issue of de-escalation, as defined  
3 above. A study of 685 patients from the MS Base registry found that switching from FTY to a  
4 platform therapy was associated with a higher relapse rate than switching to a HET.<sup>85</sup> In an  
5 observational study of 1045 patients who switched from FTY, the ARR ratio was 0.67 for OCR and  
6 2.31 for cladribine (CLA) compared to NTZ.<sup>105</sup> Thus, a “bridge” therapy with anti-CD20 agents  
7 appear as an interesting option to future de-escalation. Some neurologists propose to give a single  
8 infusion of OCR after FTY discontinuation to prevent the risk of rebound, but there are no data yet  
9 in the literature to support this strategy.

10 The wash-out duration is a challenging point. Indeed, the risk of relapse increases considerably  
11 after 2 months of wash-out,<sup>85</sup> and even after 1 month in the study of Roos et al.<sup>69</sup> High-dose  
12 corticosteroids have been proposed to bridge the washout period, especially when persistent  
13 lymphopenia prevents initiation of other treatments but this strategy has not been evaluated  
14 systematically. Finally, gradual withdrawal of FTY, with (or without) replacement by another  
15 therapy was suggested by some authors but has not really been documented to date.<sup>106</sup>

## 17 **Natalizumab**

18 Stopping NTZ without switching to another treatment is not recommended, as it is associated with  
19 a high rate of relapse or rebound. Even in the context of disease stability for 2 years or more in  
20 people over 50 treated with NTZ, discontinuation was associated with a much higher risk of relapse  
21 (HR 7.2 [95% CI 2.14-24.5, p=0.001]), in the year following treatment withdrawal compared with  
22 the continuation group (n=45 in each group).<sup>64</sup> Continuation of NTZ with extended interval dosing  
23 (EID) may be an acceptable option for patients negative for anti-JCV antibodies or positive with  
24 an index below 0.9. In fact, the efficacy on the risk of relapse appears to be maintained with 6  
25 week-dosing,<sup>107</sup> with a possible reduction in the risk of PML in anti-JCV positive pwMS.<sup>108</sup>

26 Of the 27 studies on NTZ exit strategy included in the review by Sellner et al,<sup>109</sup> most were  
27 observational. Only one looked at switching to RTX, three to DMF, nine to IFN or GA, and 18 to  
28 FTY. Overall, it appears that neither IFN nor GA are sufficient to prevent MS reactivation in the  
29 majority of patients. DMF may be an appropriate option for pwMS whose disease activity was not

1 very high before starting NTZ, although not fully protective. In a retrospective study of 506 pwMS,  
2 82% of patients were relapse-free one year after replacing NTZ with DMF.<sup>110</sup> Data on TRF as an  
3 exit strategy from NTZ are scarce. In a study of 55 pwMS switched from NTZ to TRF without  
4 washout, 77% remained relapse-free at 24 months.<sup>111</sup> Notably, in this cohort, patients under the age  
5 of 50 had a significantly higher risk of relapse. FTY is the most studied post-NTZ therapy. It has  
6 been associated with a higher relapse rate than NTZ, but lower than that seen prior to NTZ  
7 initiation.<sup>109</sup> In a study on 613 pwMS, switching to FTY was associated with a 64% reduction in  
8 the risk of relapse compared with IFN/GA.<sup>112</sup> More interesting results have been obtained by  
9 switching to anti-CD20 therapies. The study by Alping et al.<sup>113</sup> reported relapses at 1.5 years of  
10 NTZ discontinuation in 1.8% of pwMS switching to RTX (n=114) compared with 17.6% of patients  
11 switching to FTY (n=142). Similar results were observed with OCR, which was associated with a  
12 highly significant reduction in the risk of relapse at 1 year compared to FTY, with a hazard ratio of  
13 3.4 (p=0.04).<sup>114</sup> Finally, there are few data to support the use of CLA in this situation. In a study of  
14 513 pwMS who switched to CLA regardless of prior treatment, switching from NTZ was  
15 independently associated with a greater risk of relapse.<sup>115</sup> In addition, the ARR (0.5) of patients on  
16 CLA (n=20) was significantly higher than that (0.001) of patients on OCR (n=64) after NTZ  
17 discontinuation.<sup>116</sup>

18 The transient use of pulsed methylprednisolone, especially when longer washout periods are  
19 planned, has been suggested but the evidence remains limited and controversial.<sup>117,118</sup> In fact, the  
20 length of the washout period appears to be the most important factor associated with disease  
21 reactivation. It has been well shown that a washout period of less than 3 months is associated with  
22 a significantly lower risk of relapse.<sup>119</sup> There is now a consensus for very short or no washout, i.e.  
23 starting the subsequent DMT 4 weeks after the last NTZ infusion.<sup>118,120</sup> Interestingly, a tapered  
24 protocol, where participants received two injections of natalizumab at 6 and 14 weeks before  
25 switching to another DMT, was associated with lower relapse rate compared with direct  
26 switching.<sup>121</sup> Finally, regardless of the treatment and washout time chosen, the risk of carryover  
27 PML after discontinuing NTZ in JC virus-positive patients needs to be monitored with systematic  
28 MRI within 6 months of stopping.<sup>122</sup>

29

## 1 **Anti-CD20 agents**

2 In a retrospective study including 92 patients with RRMS, discontinuation of RTX for any reason  
3 was not associated with a risk of rebound or significant return of activity at 14 months of follow-  
4 up.<sup>80</sup> In the study of Jouvenot et al.,<sup>64</sup> the risk of relapse in the year after discontinuation of RTX  
5 or OCR in pwMS over 50 years of age (n=58) was similar (HR 1.1 [95% CI 0.27-4.81, p=0.852])  
6 to that of patients who continued this treatment. Thus, discontinuation of RTX and OCR may be  
7 considered in certain patients, particularly those who meet the age or disease stability criteria  
8 defined above. A RCT (NCT05285891) comparing stopping OCR at 12 or 24 months to OCR  
9 continuation in early MS is ongoing.

10 Data on switching to a platform therapy are limited. The only study compared the efficacy of a  
11 single cycle of RTX followed by GA with GA treatment from the start in 55 pwMS and showed a  
12 significant difference in several efficacy measures.<sup>123</sup> This difference decreased over time, leading  
13 the authors to suggest that the “induction” effect of RTX is limited to approximately 30 months  
14 after a single course.

15 Reducing the dose and/or extending the intervals between infusions is currently the most promising  
16 anti-CD20 de-escalation strategy. Indeed, intravenous anti-CD20 agents (RTX and OCR) are  
17 usually given every 6 months, but there is increasing evidence that their effect in MS may be much  
18 longer. Analysis of data from the OCR phase II extension trial showed that the treatment benefit of  
19 three to four 600 mg cycles on disease activity was maintained during the subsequent 18-month  
20 treatment-free period.<sup>124</sup> In a prospective cohort of 718 RTX-treated RRMS patients stratified into  
21 four infusion intervals ranging from less than 8 months to more than 18 months, no correlation was  
22 found between clinical or neuroradiological disease activity and interval duration.<sup>125</sup> In this study,  
23 kinetics of B-cell repopulation was highly variable between patients, but median total B-cell counts  
24 reached lower level of normal at 12 months and median memory B-cell counts at 16 months. In a  
25 study of 236 pwMS treated with RTX with a median interval of 17 months, the mean ARR was not  
26 different before and after the extension.<sup>126</sup> Interestingly, the level of B-cell subpopulations  
27 measured at the time of a relapse did not differ from that of patients without relapse receiving  
28 comparable dosing interval regimen. A prospective, double-arm study of 184 patients treated with  
29 OCR reported that extending the treatment interval by an average of 9 weeks and up to 78 weeks  
30 did not result in any clinical, radiological or biomarker evidence of worsening compared to

1 standard interval dosing despite higher B-cell levels.<sup>127</sup> All these findings suggest that B-cell  
2 repopulation does not correlate with the risk of return of disease activity in MS and therefore may  
3 not be a sufficient marker to guide dosing schedules. No data have been reported on extending the  
4 interval between subcutaneous injections of ofatumumab (OFA), usually given every 4 weeks.

5 The question of when infusions can be spaced by more than 6 months remains unresolved. A  
6 number of MS experts recommend dose extension after 2 years of treatment (e.g. 5 infusions) for  
7 patients with stable disease.<sup>125</sup> However, during the COVID-19 pandemic, some centres extended  
8 infusion intervals regardless of treatment duration, a decision influenced by evidence of both an  
9 increased risk of severe forms of COVID-19 and reduced efficacy of anti-COVID-19 vaccines  
10 under anti-CD20 therapy.<sup>128,129</sup> In a study of 33 RRMS patients, no disease activity was observed  
11 after RTX withdrawal for a period of 8–31 months, whatever the number of cycles previously  
12 administered.<sup>130</sup>

13 The potential benefit of EID for vaccination scheduling<sup>50,131,132</sup> or pregnancy planning is clear. One  
14 of the main goals of this strategy is also to reduce the risk of infections. EID is hypothesized to  
15 limit hypogammaglobulinemia by allowing partial repopulation of B-cells, particularly CD27<sup>+</sup>  
16 memory B-cells.<sup>126</sup> The impact of EID on the risk of hypogammaglobulinemia is emerging,<sup>133</sup> but  
17 is not yet demonstrated on the risk of infections.

18 Finally, it cannot be excluded that extending the dose interval has a negative impact on processes  
19 associated with MS progression. Indeed, a post hoc analysis of the three pivotal phase 3 trials  
20 showed that higher OCR serum concentrations were associated with a lower risk of confirmed  
21 disability progression.<sup>134</sup> The randomised trial (NCT04544436) currently underway to study safety  
22 and efficacy of a higher dose of OCR versus the approved protocol may answer this question.

23

## 24 **Immune reconstitution therapies**

25 In contrast to maintenance therapies, IRTs, which include CLA, MTX, ALZ and AHSCT, are  
26 applied once or as short intermittent courses.<sup>2</sup> The goal of IRTs is to eliminate a pathogenic immune  
27 repertoire through intense short-term immunosuppression or immune cell depletion, and to  
28 subsequently reconstitute a new immune system in the hope that immune tolerance will be  
29 restored.<sup>135</sup> Although IRTs reduce the risk of the cumulative adverse effects associated with chronic

1 immunosuppression, they expose patients to more front-loaded treatment-related risks.<sup>39</sup> Early  
2 adverse events such as febrile neutropenia and infectious complications are primarily associated  
3 with pulsed immunosuppression, late adverse events include development of secondary  
4 autoimmune disease, specifically following ALZ therapy and AHST.<sup>2</sup> De-escalation is intrinsic  
5 to the IRT approach, as sustained remission can be achieved over long periods of time.<sup>8–10,136</sup>  
6 However, disease activity and disability progression may re-emerge or continue,<sup>137,138</sup> highlighting  
7 the need for regular clinical and imaging follow-up. No evidence for MS disease activity (NEDA-  
8 3, as defined by absence of relapses, EDSS score worsening, and MRI activity) at year 2 was only  
9 achieved for 58% ALZ-treated and 44% CLA-treated patients based on data obtained in pivotal  
10 clinical trials (i.e., CARE-MS I-II and CLARITY).<sup>139–142</sup> NEDA-3 status at year 2 was reached for  
11 60-90% of pwMS following AHST using different protocols.<sup>143–146</sup> Currently, there is limited  
12 consensus about the management of patients who develop disease activity after IRTs, including re-  
13 introducing another/new DMTs or re-applying IRT modalities.<sup>147,148</sup> MTX is now much less widely  
14 used. However, it remains an interesting option as an induction drug (monthly for 6 months) before  
15 other safer long-term DMTs for patients with highly active RRMS, particularly in low-income  
16 countries. This concept was evaluated in a RCT comparing MTX followed by IFN- $\beta$  versus IFN-  
17  $\beta$  alone in 109 patients with RRMS who had experienced at least two relapses with incomplete  
18 recovery in the previous year and had CELs on MRI.<sup>7</sup> 53% of patients in the induction arm  
19 remained relapse-free at 3 years compared to 26% in the monotherapy arm ( $p<0.01$ ), and the risk  
20 of confirmed disability worsening was reduced by 65% after MTX use (12% vs. 34%).

21

## 22 **De-escalating strategies depending on specific conditions**

23

### 24 **Pregnancy**

25 Increasing evidence on drug exposure during pregnancy and lactation allow for a better benefit-  
26 risk assessment for both mother and foetus and recommendations for DMT management in this  
27 context (summarised in Table 3 and Fig. 3).<sup>101,149</sup>

1 If we consider foetal concerns, first-line injectables do not need to be discontinued before  
2 conception and can even be continued during pregnancy. Given their very short half-life and lack  
3 of evidence of teratogenicity, fumarates can be used until pregnancy is confirmed. Because of their  
4 potential teratogenicity, S1PR modulators and TRF should be stopped prior to conception, washout  
5 period depending on each treatment. Moreover, an accelerated elimination procedure is mandatory  
6 for TRF. NTZ can be continued until the end of the second trimester, even up to 30-34 weeks of  
7 gestation. During the third trimester, NTZ may increase the risk of reversible haematologic  
8 abnormalities in the newborn. EMA and FDA labels recommend avoiding pregnancy for 6 to 12  
9 months after the last anti-CD20 infusion/injection. However, since OCR and RTX do not cross the  
10 placental barrier during the first trimester and are cleared in an average of 5 months, i.e. 5 half-  
11 lives, pregnancy might be conceivable theoretically 2 months after the last infusion.<sup>149</sup> As their rate  
12 of elimination is variable,<sup>132</sup> some recommend waiting 3 to 4 months.<sup>101</sup> Similarly, OFA, with a  
13 half-life of 16 days, might be continued until pregnancy is confirmed. The main risk is the  
14 occurrence of haematological or immunological effects (and a potential contraindication for live  
15 vaccines) in neonates exposed to anti-CD20 agents during mid-or late pregnancy. Finally, for IRTs,  
16 the last dose of CLA and ALZ should be administered at least 6 months and 4 months before  
17 conception, respectively.

18 Now, considering the risk of MS reactivation or even rebound in the mother, S1PR modulators  
19 should not be stopped without replacement therapy. Anti-CD20 agents seem to be a particularly  
20 interesting “bridge therapy” in this context. CLA remains an option if pregnancy is not planned in  
21 the short term (<18 months). Less potent drugs such as IFN/GA or fumarates may be considered if  
22 disease activity prior conception was relatively low. This strategy is likely to be inferior to HETs,  
23 but better than none at all to prevent relapse.<sup>100</sup> If NTZ is continued during pregnancy (up to 30-34  
24 weeks), it is recommended that the interval between doses be extended to every 6-8 weeks and that  
25 treatment be resumed no later than 2 weeks after delivery. If NTZ is discontinued before pregnancy  
26 for any reason, bridge therapy, preferably with an anti-CD20 agent, should be initiated.

27 Modalities for resumption of DMT after childbirth are related to the issue of breastfeeding. In  
28 general, breastfeeding should not be discouraged. However, it is not compatible with restarting oral  
29 DMTs (TRF, fumarates, S1PR modulators) which are small molecules that pass into milk. Only  
30 three DMTs are officially approved for use during breastfeeding: IFN- $\beta$ , GA and OFA. Due to their  
31 high molecular weight, other anti-CD20 agents and NTZ are expected to have very limited transfer



1 to milk and to be destroyed in the digestive tract of the newborn. This has even be demonstrated  
2 for RTX.<sup>150</sup> Therefore, they can be used while breastfeeding.<sup>101,149</sup>

3

#### 4 **Paediatric-onset MS**

5 Historically, the therapeutic algorithm used in paediatric-onset MS (POMS) has been treatment  
6 escalation, starting with moderately effective DMTs and switching to HETs as needed. This  
7 strategy may reflect the lack of approved DMTs in children until recently and long-term safety  
8 concerns but may also have been influenced by the perceived better prognosis of POMS, which is  
9 sometimes thought to be associated with better recovery from relapses and a slower rate of accrual  
10 of (visible) disability compared with adult-onset MS.<sup>151</sup>

11 However, POMS is classically a more inflammatory disease than adult-onset MS, with a high  
12 degree of clinical and MRI activity. Brain atrophy has been shown to result from disease activity  
13 and can occur rapidly, especially in the first 2 years, leading to poor cognitive outcome.<sup>152</sup> Patients  
14 with POMS were shown to take approximately 10 years longer to reach irreversible disability and  
15 transition to SPMS, but they reached these milestones approximately 10 years younger than their  
16 counterparts with adult-onset disease.<sup>153</sup> In a Danish cohort of POMS (n=291), patients starting on  
17 a DMT later than 2 years after onset had a 2.52-fold increased risk of reaching sustained EDSS 4  
18 compared to those starting within 2 years of onset (HR=2.52, 95% CI=1.01-6.34).<sup>154</sup> All these  
19 factors have led to a shift towards increased use of HETs as first-line therapy in children. A recent  
20 retrospective cohort study of 530 children from the OFSEP registry found that initial HET resulted  
21 in a 54% reduction in the risk of relapse within 2 years compared with moderately effective  
22 therapies.<sup>155</sup> Therefore, DMT discontinuation during childhood is not recommended. However, the  
23 issue of de-escalation in adult patients with POMS is emerging, particularly if HETs are used more  
24 often and earlier. Young subjects will indeed be exposed to treatments for a longer period, and we  
25 still lack data on long-term effects on fertility, infectious and oncological risks, particularly in the  
26 case of cumulative exposure. Long-term studies involving paediatric and adult MS providers are  
27 therefore needed. Recent and limited data are now available on EID strategies for anti-CD20  
28 antibodies, suggesting that the efficacy of RTX/OCR could be maintained with a median EID of

1 18 months (observational study of 21 POMS cases, median age 16 years, median follow-up of 31  
2 months).<sup>156</sup>

3

#### 4 **Monitoring of de-escalation in MS**

5 After de-escalation, MS activity and progression need to be monitored in a multidimensional and  
6 systematic way. In the four RCTs investigating de-escalation (2 completed, 2 ongoing), different  
7 outcomes have been selected: i) clinical outcomes assessing the occurrence of relapses and  
8 neurological disability (EDSS, MS functional composite [MSFC]), ii) radiological outcomes with  
9 brain MRI (no systematic spinal cord MRI, only in case of medullary relapse in STOP-I-SEP), iii)  
10 biological outcomes with blood NfL level in TWINS and DOT-MS, iv) patient-related outcomes  
11 (PROs) regarding quality of life, anxiety and depression, and treatment burden.

12 General recommendations could be proposed regardless of the age of the patient, disease duration,  
13 phenotype and severity of MS and type of DMT. Patients should be monitored with clinical  
14 outcomes assessing the occurrence of relapses and neurological disability (EDSS, and a  
15 multidimensional functional capacity test such as MSFC), ideally complemented by PROs.  
16 Baseline brain and spinal cord MRI is recommended at de-escalation. However, the frequency and  
17 duration of the radiological monitoring should be tailored to each situation. After de-escalation of  
18 a platform therapy in a stable elderly patient, we might recommend a brain and spinal cord MRI  
19 12 months after discontinuation. On the other hand, after stopping an anti-cell trafficking treatment  
20 such as NTZ or FTY, brain and spinal cord MRI should be performed earlier, at 3 and/or 6 months  
21 because of the risk of rebound (and PML). Nevertheless, the exact number of new T2 lesions to  
22 define radiological activity is not clearly defined (at least one in DISCO-MS; at least 3 and/or CELs  
23 in DOT-MS and TWINS) and should be tempered by the individual situation.

24 The interest for digital measures in the management of pwMS emerged a few years ago.<sup>157</sup> They  
25 could potentially assess various symptoms in the patient's ecological environment and allow to  
26 follow the insidious progression of disability. The value of their use in monitoring de-escalation  
27 needs to be assessed.

1 In recent years, biological markers have been identified in MS. In particular, serum NfL is strongly  
2 associated with disease activity and treatment effectiveness,<sup>158</sup> but its physiological age-dependent  
3 increase may limit the diagnostic use of this biomarker at the individual level.<sup>159</sup> On the other hand,  
4 GFAP is correlated with disease progression, in CSF<sup>160</sup> and even in serum.<sup>161</sup> To date, only one  
5 study has evaluated changes in serum NfL and GFAP levels after treatment discontinuation of  
6 treatment in 78 patients.<sup>162</sup> In this study, increasing levels of either sNfL or sGFAP after stopping  
7 treatment were associated with a higher risk of 6-month confirmed disability worsening and  
8 developing a new MRI lesion, but not with a new clinical relapse. Therefore, the usefulness and  
9 routine feasibility of monitoring these biomarkers after de-escalation need further investigation.  
10 For this purpose, MultiSCRIPT is an ongoing Swiss RCT (NCT06095271) that will assess whether  
11 sNfL monitoring is helpful in guiding personalised decisions about DMTs in people with RRMS.  
12

## 13 **Conclusion and future directions**

14 Over a patient's lifetime, the natural course of MS changes, with fewer relapses and MRI activity  
15 and a greater risk of progression. The same applies to the benefit-risk ratio of currently available  
16 DMTs, which becomes less favourable with age and needs to be reassessed regularly.

17 The age of the patient is therefore the most important criterion for considering de-escalation.  
18 Although there is no consensus, the cut-off age seems to be at least 55 years and perhaps even  
19 older. Prudent de-escalation also requires no clinical or radiological evidence of disease activity  
20 for several years, on average five. The results of further randomised trials are needed to confirm  
21 these thresholds.

22 Besides these common criteria, the decision must take into account factors specific to each patient,  
23 such as their willingness, as well as conditions (severe disability, comorbidities, JCV status,  
24 hypogammaglobulinemia, among others) that may increase the risks of treatment. In all cases, the  
25 decision must be a shared process between patients and physicians.

26 The de-escalation strategy depends mainly on the type of DMT used, and in particular on its  
27 potential risk of rebound. There is increasing evidence supporting dose-spacing strategies for  
28 monoclonal antibodies. Other interesting approaches have been proposed but are currently being

1 evaluated. These include the use of a single infusion of anti-CD20 after stopping NTZ or an S1PR  
2 modulator, or the use of CLA as an exit therapy in older patients.

3 There is also no consensus on the nature, frequency and duration of monitoring after de-escalation,  
4 except that it is mandatory. De-escalation is not a cessation of care and should not be perceived as  
5 such by the patient. Future efforts are warranted to assess the impact of DMT de-escalation on  
6 safety outcomes as well as on disease progression, particularly on less visible parameters such as  
7 fatigue or cognitive impairment. In this context, biomarkers and PROs which can be used in clinical  
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9

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# 1 **Figure Legends**

2  
3 **Figure 1 Rationale for de-escalation in multiple sclerosis.** PIRA: progression independent of  
4 relapse activity. \*The benefit-risk ratio may be influenced by individual factors (cf. Fig. 2).

5  
6 **Figure 2 Main factors influencing the benefit-risk balance of long-term DMTs.** COPD:  
7 chronic obstructive pulmonary disease; DMF: dimethylfumarate; DMTs: disease-modifying  
8 therapies; JCV: John Cunningham virus; HPV: human papillomavirus; NTZ: natalizumab; OCR:  
9 ocrelizumab; RTX: rituximab; S1PRM: sphingosine-1-phosphate-receptor modulators.

10  
11 **Figure 3 Main de-escalation scenarios depending on DMT subtypes.** EDSS: Expanded  
12 Disability Status Scale; DMT: disease-modifying therapies, IRT: immune reconstitution therapy;  
13 R/B: benefit-risk; y: years. \*Proposed cut-off, take also into account disease duration

14  
15 **Figure 4 De-escalation strategies in the context of pregnancy planning.** GA: glatiramer  
16 acetate, IRT: immune reconstitution therapy; S1PR: sphingosine-1-phosphate receptor.

ACCEPTED MANUSCRIPT

Table 1 Main studies published in the last 5 years on treatment discontinuation in multiple sclerosis

Reference	Study type	Study and size of the population	Criteria of discontinuation			Type of DMTs	Follow-up time	Outcomes	Results
			Age	No relapse	No MRI activity				
Jouvenot <i>et al.</i> <sup>64</sup>	Retro Obs	RR, SP N = 308 154 C / 154 D	≥50 y	≥2 y	≥2 y	HET ≥1 y	3 y (D) 1.9 y (C)	Time to first relapse	HR of relapse of 4.14 in D versus C (p=0.0001); HR 4.48 FTY, 7.25 NTZ, 1.15 anti-CD20
Chappuis <i>et al.</i> <sup>65</sup>	Retro Obs	RR, SP, PP 232 D	≥45 y median 52.8 y	NA	NA	183 platform 49 HET	6.4 y	Risk of relapse in the 1st year	6% platform, 9% FTY, 43% NTZ
							4.2 y		
Corboy <i>et al.</i> <sup>66</sup>	RCT	RR, SP, PP N = 259 128 C / 131 D	≥55 y median 63 y	≥5 y	≥3 y	73% IFN or GA	2 y	Combined criterion (relapse and MRI)	Non inferiority not demonstrated
								% relapse	Non inferiority demonstrated: 0.78% (C) versus 2.29% (D)
								% MRI activity	Non inferiority not demonstrated: 3.91% (C) versus 10.79% (D)
Zanga <i>et al.</i> <sup>67</sup>	Retro Obs	RR, active SP N=377 D	NA	NA	NA	Unknown	16 mo	Frequency of disease activity	19% relapse RR, 3.5% SP 22% MRI activity RR, 3.5% SP
								Risk factors	Age <45 y, shorter disease duration, RR MS, male sex
Jakimowski <i>et al.</i> <sup>68</sup>	Retro Obs	RR, SP N=216 D	NA mean 50.6 y	NA	NA	IFN, GA, NTZ, MTX, off-label	4.6 y	Clinical course	Disability progression in 32.9% of previously stable patients, not influenced by age <or ≥55 y
Roos <i>et al.</i> <sup>69</sup>	Retro Obs	RR N = 14 213 D	NA	NA	NA	Platform, FTY, NTZ, MTX	≥1 y	Predictors of relapse	Higher relapse rate in the year before, female sex, younger age, higher EDSS score, NTZ of FTY cessation
Bsteh <i>et al.</i> <sup>70</sup>	Retro	RR N=266 D	<45 y (2pts) ≥45 y <55y (1 pt) ≥55 y (0 pt)	<4 y (2 pts) ≥4 y <8 y (1 pt) ≥8 y (0 pt)	≥3 new T2 or ≥1 Gd+ (2 pts) <3 new T2 and no Gd+ (0 pt)	IFN, GA	≥2 y	Validation of a score predicting the risk of reactivation (VIAADISC)	Low risk (score 0-1) = 7% risk of disease reactivation within 5 y Intermediate risk (score 2-3) = 36-38% High risk (score 4-5) = 83-85%
McFaul <i>et al.</i> <sup>71</sup>	Retro Obs	'benign/burnt-out RR MS' N = 136 D	≥50 y mean 60.6 y	Mean time since last relapse 11 y	NA	96% IFN or GA	Mean 5 y	Disease outcomes	3.7% relapse, 2.2% MRI activity
								Risk factors	Age only
Pasca <i>et al.</i> <sup>72</sup>	Retro Obs	RR N = 60 D	NA mean 48 y	NA	NA	IFN, GA, AZA, DMF	Mean 5.2 y	Disease outcomes	No increase of relapse rate or MRI activity
								Protective factor	NEDA-3 > 5.5 y before DMT cessation
Kaminsky <i>et al.</i> <sup>73</sup>	Retro Obs	RR, SP N = 498 366 C / 132 D	>50 y	≥3 y	NA	99% IFN or GA	Mean 7.7 y	Time to first relapse	NS
								Time to progression	NS
								Occurrence of EDSS 6	aHR = 3.29 (p <0.0001) for D versus C
Hua <i>et al.</i> <sup>58</sup>	Retro Obs	RR, SP, PP N= 600 422 C / 178 D	≥60 y	NA	NA	Platform, FTY, NTZ, MTX, off-label	2 y	Clinical and patient-reported outcomes	Only one relapse in 178 D No difference in functional scores between D and C

									Better quality of life in D
Yano et al. <sup>74</sup>	Retro Obs	RR N = 138 69 D / 69 C	≥18 y	≥2 y	≥2 y	IFN, GA, FTY, NTZ	≥2 y	Time to first relapse / to first MRI event	No significant difference between D and C except if age ≤ or >45 y

aHR = adjusted hazard ratio; C = continuers; CEL = contrast-enhancing lesion; D = discontinuers; DMF = dimethylfumarate; DMT = disease-modifying therapy; EDSS = expanded disability status scale; FTY = fingolimod; GA = glatiramer acetate; HETs = high-efficacy therapies; HR = hazard ratio; IFN = interferon beta; MS = multiple sclerosis; MTX = mitoxantrone; mo = months; NA = not applicable; NEDA = no evidence of disease activity; NTZ = natalizumab; Obs = observational; OCR = ocrelizumab; PP = primary progressive; RCT = Randomised Controlled Trial; Retro = retrospective; RR = relapsing-remitting; RTX = rituximab; SP = secondary progressive; TRF = teriflunomide; y = years.

**Table 2 De-escalation strategies according to disease-modifying treatment subtype**

DMT subtype	Risk of rebound	Stopping	Dosing interval extension / dose reduction	Switch strategies
<b>Platform therapies</b>				
IFNβ, GA, TRF, DMF/DRF	No	Possible	Not investigated	Not justified
<b>Anti-trafficking therapies</b>				
SIPR agonists	Yes	Not recommended	Tapered withdrawal suggested (not yet supported by strong data)	<b>Switch options:</b> Platform therapies: not recommended (TRF and DMF/DRF possible in patients with relatively low pre NTZ activity) Anti-CD20 agents: interesting (a single course of intravenous anti-CD20 infusion might be discussed) Cladribine: possible but potentially less effective than anti-CD20 <b>Wash-out period as short as possible</b> (<2 months and ideally ≤1 month) <b>Beware of carryover PML</b>
Natalizumab	Yes	Not recommended	Dosing interval ≤ 6 weeks if JCV status negative (or index < 0.9)	
<b>Anti-CD20 agents</b>	No	Possible	Possible and supported by real world data for rituximab and ocrelizumab (RCTs ongoing) Lack of data for ofatumumab	Switch to platform therapies: possible but limited data
<b>IRT</b>				
Cladribine, Alemtuzumab, AHST, Mitoxantrone	No	Yes = part of the mechanism of action	Usually not applicable	Not systematic, to be discussed case by case if subsequent disease reactivation.
Mitoxantrone	No	Yes = part of the mechanism of action	Usually not applicable	3-6 months after the last dose, switch to platform therapies

AHST = autologous hematopoietic stem cell transplantation; DMF = dimethylfumarate; DMT = disease-modifying therapy; DRF = diroximel fumarate; GA = glatiramer acetate; IFNβ = interferon beta; IRT = immune reconstitution therapies; JCV = John Cunningham virus; NTZ = natalizumab; PML = progressive multifocal leukoencephalopathy; RCTs = randomised controlled trials; SIPR = sphingosine-1-phosphate receptors; TRF = teriflunomide.

1 **Table 3 Guidelines for managing multiple sclerosis disease-modifying treatment in the context of pregnancy planning**

DMT subtype	Maintenance up to conception <i>If not, minimum time from last dose</i>	Maintenance during pregnancy	Bridge therapy	Breastfeeding
<b>IFN <math>\beta</math> and GA</b>	Yes	Possible, depending on pre-treatment activity	Not necessary	Possible
<b>TRF</b>	No $\geq 24$ months or accelerated elimination procedure (recommended)	No	Possible if justified	Contraindicated
<b>DMF/DRF</b>	Yes	No Stop when confirmed pregnancy	Not necessary	Not recommended
<b>SIPR modulators</b>	No	No	Strongly recommended <b>During pregnancy planning period:</b> Anti-CD20 agents <sup>a</sup> : in priority Cladribine <sup>a</sup> , NTZ: may be considered IFN $\beta$ /GA, DMF/DRF: possible but potentially less effective	Contraindicated
Fingolimod	$\geq 2$ months			
Ozanimod	$\geq 3$ months			
Ponesimod	$\geq 1$ week			
Siponimod	$\geq 10$ days		<b>If pregnancy started while on treatment:</b> depending on pre-treatment activity, NTZ or IFN $\beta$ /GA can be considered	
<b>Natalizumab</b>	Yes	Possible until the end of the second trimester (even up to 30-34 weeks of gestation, depending on pre-treatment activity) Extended interval dosing recommended (6-8 weeks)	<b>During pregnancy planning period:</b> possible ( <i>alternative scenario to maintenance</i> ) Anti-CD20 agents <sup>a</sup> : in priority Cladribine <sup>a</sup> : may be considered IFN $\beta$ /GA, DMF/DRF: possible but potentially less effective <b>If pregnancy started while on treatment:</b> not recommended, maintain NTZ until 30-34 weeks of gestation	Possible
<b>Anti-CD20 agents</b>				
RTX / OCR	Not recommended $\geq 2-3$ months	No, unless absolutely needed	Not necessary	Possible
Ofatumumab	Possible	No, unless absolutely needed	Lack of data	
<b>IRTs</b>	No	No	No	Contraindicated during treatment
Cladribine	$\geq 6$ months (women and men), ideally after the 2nd treatment cycle			Possible $\geq 1$ week after last dose
Alemtuzumab	$\geq 4$ months, ideally after the 2nd treatment cycle			Possible $\geq 4$ months after last dose
Mitoxantrone	$\geq 6$ months (women and men)			Possible $\geq 1$ month after last dose

Underline emphasises the risk in the event of paternal exposure, which is less well known. DMF = dimethylfumarate; DMT = disease-modifying therapy; DRF = diroximel fumarate; GA = glatiramer acetate; IFN  $\beta$  = interferon beta; IRTs = immune reconstitution therapies; JCV = John Cunningham virus; NTZ = natalizumab; OCR = ocrelizumab; RTX = rituximab; SIPR = sphingosine-1-phosphate receptors; TRF = terflunomide.  
<sup>a</sup>Conception should be planned according to the respective recommendations for these molecules.

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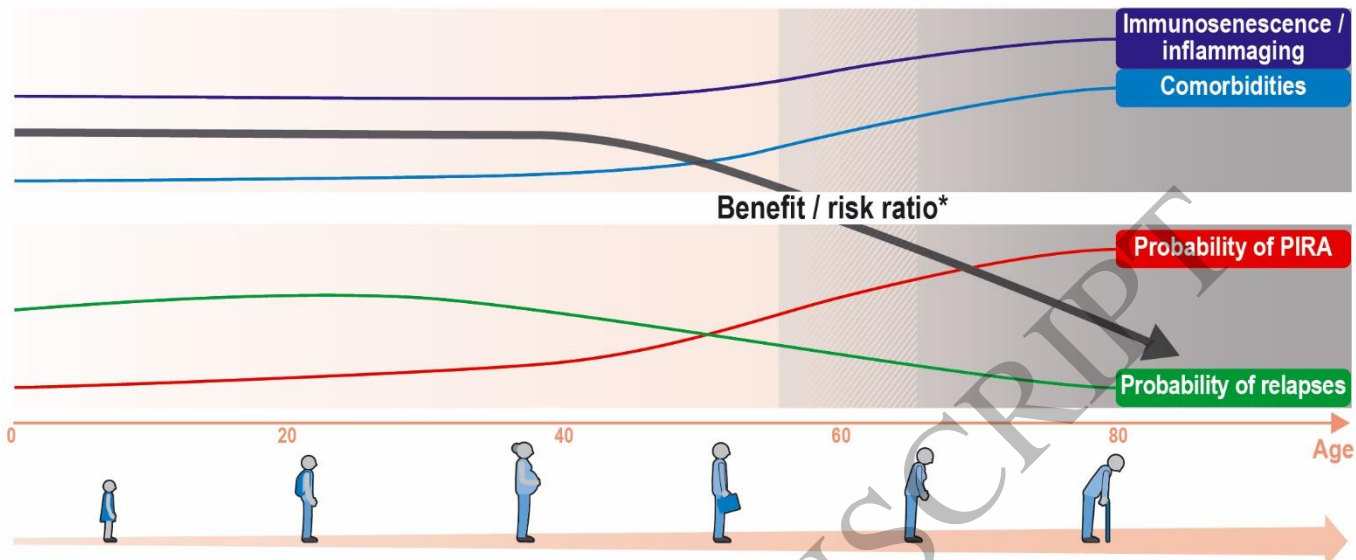


Figure 1  
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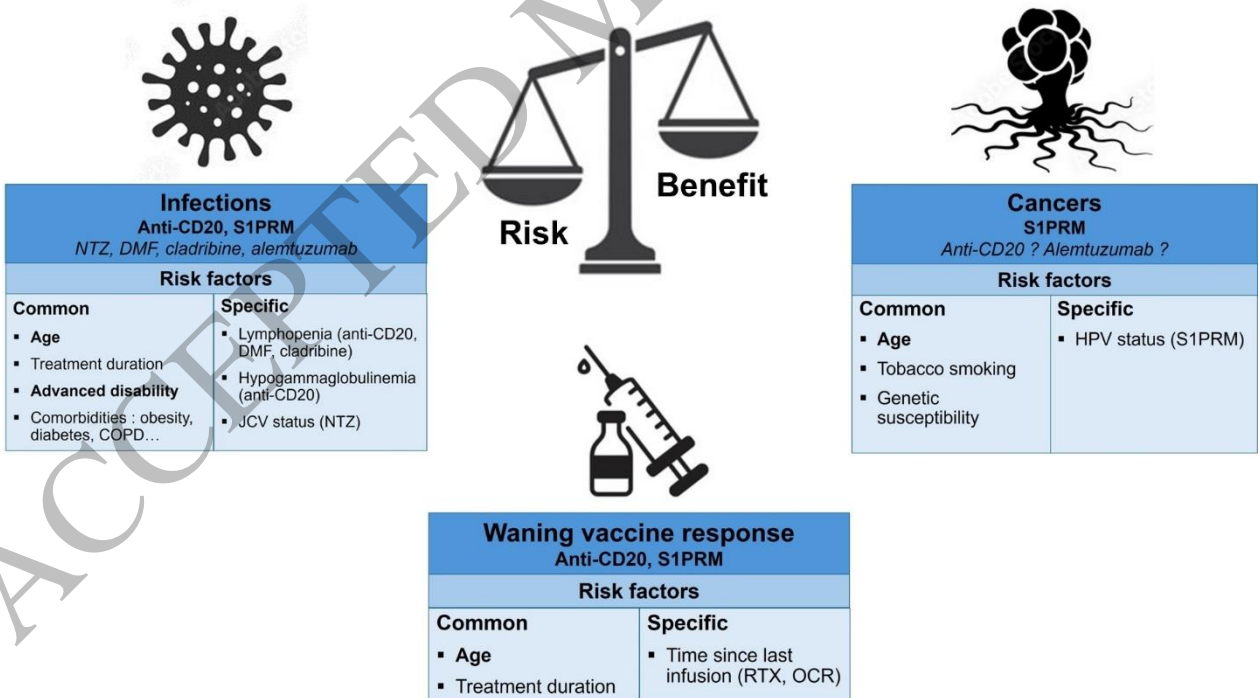


Figure 2  
322x187 mm (DPI)

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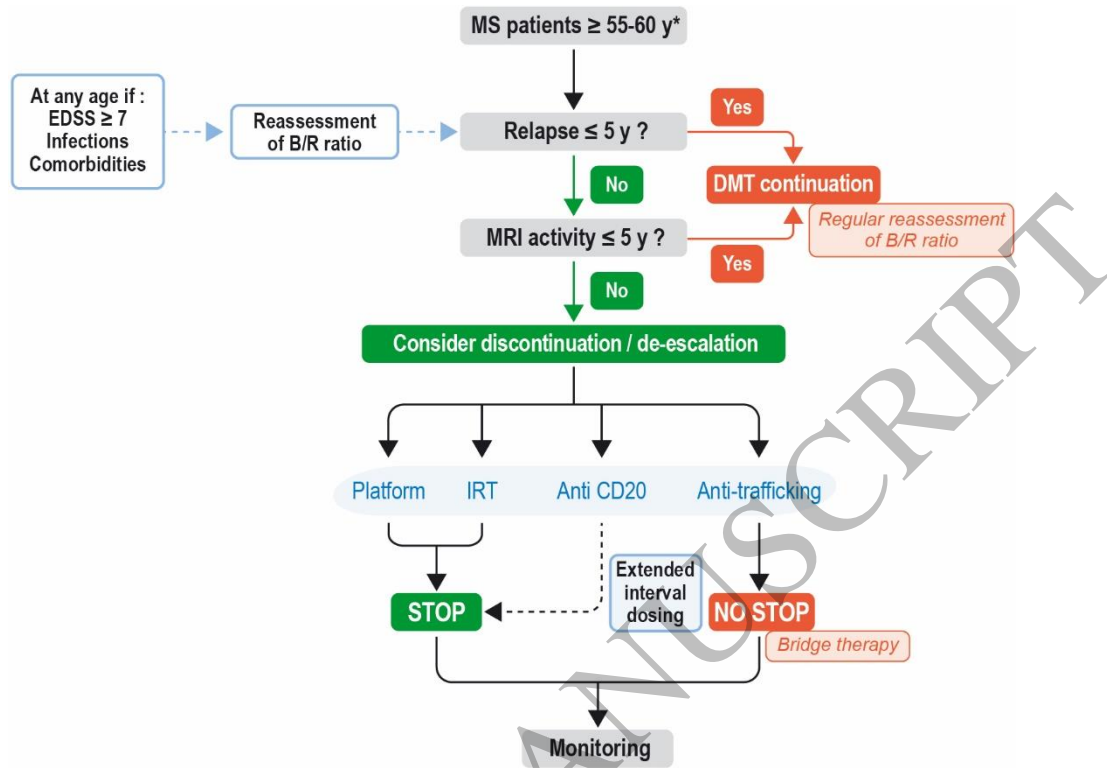


Figure 3  
133x101 mm (DPI)

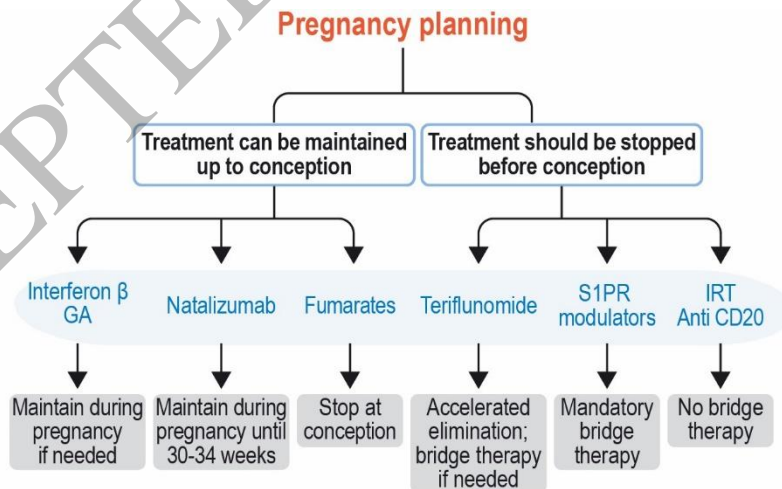


Figure 4  
108x65 mm (DPI)

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