REVIEW ARTICLE

De-escalating and discontinuing disease-modifying therapies in multiple sclerosis

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Abstract

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

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

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Running title: De-escalation in MS

Keywords: multiple sclerosis; disease-modifying therapy; de-escalation; discontinuation; aging; pregnancy

Introduction

Disease-modifying therapies (DMTs) for the treatment of multiple sclerosis (MS) have developed considerably over the last 30 years; their goal has gradually shifted from reducing relapse rates to achieving complete control of the peripherally-mediated inflammatory component of the disease.[1,2] Therapeutic algorithms are continuously being refined, and it is now broadly accepted that greater benefits of DMTs, in terms of relapse prevention and delayed progression, can be achieved if an appropriately effective treatment is initiated early after disease onset.[3,4] The selection of DMTs is guided by a benefit-risk assessment, fed by the debate between escalation and early high-efficacy therapeutic regimens.[5,6] Most of MS DMTs are given continuously. These maintenance therapies include molecules known as "platform therapies": interferon-β (IFN-β), glatiramer acetate (GA), teriflunomide (TRF), dimethyl fumarate (DMF)/ diroximel fumarate (DRF), as well as "high-efficacy therapies" (HETs), including anti-CD20 antibodies and drugs targeting the traffic of

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

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

The scope of de-escalation strategies

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

The rationale for de-escalation

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

Immunosenescence, inflammaging and their relevance to MS pathogenesis

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

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

by microglial activation and meningeal infiltration.[21] Both processes correlate with diffuse neuroaxonal loss, which is thought to be the main substrate of progressive disability in MS.[22,23]

Thus, pwMS may acquire disability either through relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA).[24] Recently, PIRA has been shown to start early in the disease process, even in RRMS, and to become the main driver of disability accumulation with increasing age and disease duration.[24,25] Age has long been suspected to play a role in the pathogenesis of progression, as the median age at onset of the progressive phase was similar in SP and PP patients, between 40 and 45 years.[26,27]

Therefore, ISe and IA may play a role both in the decrease of focal inflammatory activity and the progressive neurodegeneration observed with increasing age in MS and in the variation of efficacy and risks of DMTs (Fig 1).[28]

Efficacy issues

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

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

score matching showed that ocrelizumab (OCR) still significantly reduced the annualized relapse rate (ARR) by a ratio of 0.15 compared with IFN-β /GA in pwMS over 60 years of age (n=248 and 427 respectively).[33]

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

Safety issues

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

other anti-CD20 drugs, although long term follow-up of the pivotal OCR studies does not seem to support a significantly higher risk of infections.[43]

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

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

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

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

Patients' willingness

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

Economic and regulatory considerations

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

The potential risks of treatment de-escalation in MS

Risk of disease reactivation

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

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

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

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

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

Risk of rebound

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

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

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

Risk of accelerated progression

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

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

Risk of poor recovery of relapse with aging

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

Patient concerns

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

Main de-escalation scenarios in adult patients with MS

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

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

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

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

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

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

patients and their partners, and anticipated as far as possible.[70,101] Importantly, any DMT choice for a woman of childbearing age must take into account her family planning.

De-escalating strategies depending on DMT types

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

Platform therapies

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

Fingolimod (and by extension other S1PR modulators)

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

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

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

Natalizumab

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

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

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

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

Anti-CD20 agents

In a retrospective study including 92 patients with RRMS, discontinuation of RTX for any reason was not associated with a risk of rebound or significant return of activity at 14 months of follow-up.[80] In the study of Jouvenot et al.,[64] the risk of relapse in the year after discontinuation of RTX 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]) to that of patients who continued this treatment. Thus, discontinuation of RTX and OCR may be considered in certain patients, particularly those who meet the age or disease stability criteria defined above. A RCT (NCT05285891) comparing stopping OCR at 12 or 24 months to OCR continuation in early MS is ongoing.

Data on switching to a platform therapy are limited. The only study compared the efficacy of a single cycle of RTX followed by GA with GA treatment from the start in 55 pwMS and showed a significant difference in several efficacy measures.[123] This difference decreased over time, leading the authors to suggest that the "induction" effect of RTX is limited to approximately 30 months after a single course.

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

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

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

The potential benefit of EID for vaccination scheduling[50,131,132] or pregnancy planning is clear. One of the main goals of this strategy is also to reduce the risk of infections. EID is hypothesized to limit hypogammaglobulinemia by allowing partial repopulation of B-cells, particularly $CD27^{+}$ memory B-cells.[126] The impact of EID on the risk of hypogammaglobulinemia is emerging,[133] but is not yet demonstrated on the risk of infections.

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

Immune reconstitution therapies

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

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

De-escalating strategies depending on specific conditions

Pregnancy

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

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

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

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

to milk and to be destroyed in the digestive tract of the newborn. This has even be demonstrated for RTX.[150] Therefore, they can be used while breastfeeding.[101,149]

Paediatric-onset MS

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

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

18 months (observational study of 21 POMS cases, median age 16 years, median follow-up of 31 months).[156]

Monitoring of de-escalation in MS

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

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

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

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

Conclusion and future directions

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

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

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

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

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

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

Acknowledgements

Mrs Alena Herbstritt and the Congrex team for organising the workshop.

Funding

No specific funding, apart from European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) funding for the organisation of the focused workshop in Lisbon on 9-10 March 2023.

Competing interests

GA has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen, Jannsen, Merck, Novartis, Roche and Sanofi-Genzyme.

JDL has received honoraria for acting as a member of Scientific Advisory Boards for Abbvie, Alexion, Argenx, Moderna, Sanofi and Takeda as well as speaker honoraria and travel support from Alexion, Argenx, Biogen, Roche Pharma AG, Merck, Moderna, Novartis, and Sanofi. His research is funded by the European Union, Deutsche Forschungsgesellschaft (DFG), Alexion, Argenx, Moderna, and Roche Pharma AG.

EM reports research support from Biogen and ARSEP foundation and personal fees for lectures and advisory boards from Biogen, Janssen, Merck, Novartis, Roche, Sanofi, Teva.

MPA has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen, Jannsen, Merck, Novartis, Roche, Sanofi-Genzyme, Sandoz and Celgene BMS, and research grants by Novartis, Merck and Roche.

GB has participated in meetings sponsored by, received speaker honoraria or travel funding from Biogen, Celgene/BMS, Janssen, Lilly, Merck, Novartis, Roche, Sanofi-Genzyme and Teva, and received honoraria for consulting Biogen, Celgene/BMS, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva. He has received unrestricted research grants from Celgene/BMS and Novartis.

HB received institutional (Monash University) funding from Biogen, Hoffmann-La Roche Ltd, Merck, UCB, TEVA and Novartis for research projects, speaker honoraria and steering committee activities. He has received travel support from Novartis and Merck.

OC: NIHR Research Professor (RP-2017-08-ST2-004); over the last 2 years, member of independent DSMB for Novartis; she gave a teaching talk in a Merck local symposium, and contributed to an Advisory Board for Biogen; she is Deputy Editor of Neurology, for which she receives an honorarium; she has received research grant support from the MS Society of Great Britain and Northern Ireland, the NIHR UCLH Biomedical Research Centre, the Rosetree Trust, the National MS Society, and the NIHR-HTA.

ACC has received grant from Instituto de Salud Carlos III, Spain; JR19/00007.

TD received speaker fees, research support, travel support, and/or served on Advisory Boards or Steering Committees of Alexion, Novartis, Merck, Biogen, GeNeuro, MedDay, Roche, and Sanofi Genzyme.

FDP has participated in meetings sponsored by, received honoraria (lectures, advisory boards, consultations) or travel funding from Amgen, Bayer, Biogen, Celgene, Horizon, Merck, Novartis, Sanofi-Genzyme, Roche and Teva.

GE is the technical and scientific coordinator (RST) of the RHU Primus since 2021, having a partnership with the industrials Merck, Biogen, Pixyl for this research and economic program.

CE has received personal compensation for consulting or speaking from Biogen-Idec, BMS, EMD-Serono, Novartis, Roche, and Sanofi-Genzyme.

RG received support for scientific meetings and courses from Bayer, Biogen, Merck, Novartis, Jasen and honoraria for advisory work or talks from Biogen, Novartis, UCB, MIAC.

CG: The University Hospital Basel (USB) and the Research Center for Clinical neuroimmunology and Neuroscience (RC2NB), as the employers of Cristina Granziera, have received the following fees which were used exclusively for (research support from Siemens, GeNeuro, Genzyme-Sanofi, Biogen, Roche. They also have received advisory board and consultancy fees from Actelion, Genzyme-Sanofi, Novartis, GeNeuro, Merck, Biogen and Roche; as well as speaker fees from Genzyme-Sanofi, Novartis, GeNeuro, Merck, Biogen and Roche.

HPH received honoraria for serving on SC, DMC or speaking at symposia from Biogen, BMS Celgene, Merck, Novartis, Roche, Sanofi, TG Therapeutics; for work as section chief editor of Frontiers Neurology / Immunology.

MI has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Alexion, Biogen, Brystol Meyer Squibb, Janssen, Merck, Novartis, Roche and Sanofi-Genzyme.

LK: Ludwig Kappos' institutions (University Hospital Basel and RC2NB) have received compensation that was used exclusively to support research, for the following: consultancy fees from Bayer HealthCare, Biogen, Bristol Myers Squibb, Celltrion Inc., Eli Lilly SA, EMD Serono Research and Development, GlaxoSmithKline, Galapagos NV, Janssen, Japan Tobacco Inc., Kiniksa Pharmaceuticals, Merck Healthcare AG, Minoryx, Neurostatus UHB AG, Novartis, Roche, Sanofi, Santhera Pharmaceuticals, Shionogi BV, Wellmera AG, and Zai Lab; contracted research from the European Union, InnoSwiss, Merck Healthcare AG, Novartis, Neurostatus UHB AG, Sanofi, and Roche; speaker fees and support of educational activities from Bristol Myers Squibb, Janssen, Roche, Sanofi, Merck, and Novartis; serving on the steering committee or advisory board for Biogen, EMD Serono Research and Development, Genentech, Janssen, Novartis, Clene Nanomedicine Inc., and Sanofi.

HK has received personal compensation for consulting, serving on a scientific advisory board, speaking, or participated in clinical trials from Merck, Sanofi, Novartis, Roche, Celgene, Jansen Cilag, Biogen, Sandoz, Argenx and Alexion. Research funding from Academy of Finland Strategic Research Council (31213358415) and the State funding for university-level health research, Tampere University Hospital, Finland (9AC042).

ALG has received grant support and awards from the Patient-Centered Outcomes Research Institute, the National MS Society, and Atara Biotherapeutics. She currently serves as a voting member on the California Technology Assessment Forum, a core program of the Institute for Clinical and Economic Review (ICER).

MM served on scientific advisory board, as consultant for, received support for congress participation or speaker honoraria from Biogen, Sanofi, Roche, Novartis, Merck, Alexion and Bristol Myers Squibb. The Danish MS Registry received research support from Biogen, Genzyme, Roche, Merck and Novartis.

RM serves on scientific advisory boards for Amgen/Horizon Therapeutics, UCB and Roche; and has received funding for travel and fees from Amgen, Alexion, Biogen, Roche.

XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic Therapeutics, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

MPM has received speaking fees from Sanofi, Biogen, Merck, Serono, Novartis, Roche, Boehringer Ingelheim, Bristol Myers Squibb and Teva.

BN has received research funding from the US National Multiple Sclerosis Society, the US National Institutes of Health, the US Department of Defense, PCORI, Genentech, and Axsome Therapeutics. He has received consulting honoraria from TG Therapeutics and Alkermes.

JO has received grant funding from Brain Canada, MS Canada, the National MS Society, Biogen-Idec, Roche, and EMD-Serono and has received personal compensation for consulting or speaking from: Biogen-Idec, BMS, EMD-Serono, Eli-Lilly, Horizon Therapeutics, Novartis, Roche, and Sanofi-Genzyme.

COG has received speaking and/or consultancy fees from Alexion, Biogen, BMS, Jannsen, Merck, Novartis, Roche, Sanofi, and Teva.

FP has received research grants from Janssen, Merck KGaA and UCB, and fees for serving on DMC in clinical trials with Chugai, Lundbeck and Roche, and preparation of expert witness statement for Novartis.

LP has received personal fees and non-financial support from Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi and Viatris.

JSG received compensation in the last 24 months for consulting services and speaking honoraria from BMS, Sanofi, Merck, Janssen, Novartis, and Roche, is scientific director of Revista de Neurología and member of the editorial committee of Multiple Sclerosis Journal, for which he receives an honorarium. He has received research support from Fondo de Investigación en Salud (PI19/00950 and PI22/00750) from Instituto de Salud Carlos III, Spain.

FS has served on scientific advisory boards for, served as consultant for, received support for congress participation or received speaker honoraria from Biogen, Bristol Myers Squibb, Lundbeck, Merck, Novartis, Roche and Sanofi Genzyme, and has received research support from Biogen, Merck, Novartis, Roche and Sanofi Genzyme for his laboratory.

KS has received personal compensation for consulting from Biogen, Celgene, GeNeuro, Merck, Novartis, Polpharma, Sanofi, Roche, TG Therapeutics, and received research support from Merck and Roche

AS has received research grants from The Turkish Multiple Sclerosis Society; and research grants from The Scientific and Technological Research Council Of Turkey & Istanbul University-Cerrahpasa Research Support Funds and has received honoraria or consultancy fees for participating to advisory boards, giving educational lectures and/or travel and registration coverage for attending scientific congresses or symposia from F. Hoffmann-La Roche Ltd, Merck-Serono, Novartis, Teva, Biogen Idec/Gen Pharma of Turkey, Alexion, Abdi Ibrahim Ilaç and Ali Raif Ilaç.

ET has received honorarium for consulting work from Biogen, Janssen, Merck, Novartis, and Roche in the last 5 years. She has received travel grants to attend or speak at educational meetings from Biogen, Merck, Roche, Takeda and Novartis.

VvP received travel grants from Merck Healthcare KGaA (Darmstadt, Germany), Biogen, Sanofi, Bristol Meyer Squibb, Almirall and Roche. His institution has received research grants and

consultancy fees from Roche, Biogen, Sanofi, Merck Healthcare KGaA (Darmstadt, Germany), Bristol Meyer Squibb, Janssen, Almirall, Novartis Pharma, and Alexion.

SV has received non-personal consulting and lecturing fees, travel grants and unconditional research support from Biogen, Janssen, Merck, Novartis, Roche, Sandoz and Sanofi.

BWG served as a consultant for Biogen, EMD Serono, Novartis, Genentech, Celgene/Bristol Meyers Squibb, Sanofi Genzyme, Bayer, Janssen, Labcorp , Horizon and SANA. She also has received grant/research support from Novartis, Biogen and Horizon/Amgen. She serves in the editorial board for Children, CNS Drugs, MS International, Journal of Neurology and Frontiers Epidemiology.

FZ has recently received research grants and/or consultation funds from Biogen, German Ministry of Education and Research (BMBF), Bristol-Meyers-Squibb, Celgene, German Research Foundation (DFG), Janssen, Max-Planck-Society (MPG), Merck Serono, Novartis, Progressive MS Alliance (PMSA), Roche, Sanofi Genzyme and Sandoz.

MT has received compensation for consulting services, speaking honoraria and research support from Almirall, Bayer Schering Pharma, Biogen-Idec, Genzyme, Immunic Therapeutics, Janssen, Merck-Serono, Novartis, Roche, Sanofi-Aventis, Viela Bio and Teva Pharmaceuticals. Data Safety Monitoring Board for Parexel and UCB Biopharma, Relapse Adjudication Committee for IMCYSE SA.

EI has received honoraria for serving on advisory boards for Biogen, Sanofi-Genzyme, and Merck and speaker's fees from Biogen and Sanofi-Genzyme. She has received unrestricted research grant from Sanofi-Genzyme and research funding from Region Stockholm Clinical Research Appointment, Neuro Sweden and the Lindholm Fredholms foundation.

BS has received lecturing fees, from Biogen Idec, Merck-Serono, Novartis, Sanofi, Janssen, and unconditional research support (to the institution) from Merck-Serono, Novartis, and Roche. BA, ALB, YH, SH report no competing interests.

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Figure Legends

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

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

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

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

1 **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 *et al.*[64]	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 *et al.*[65]	Retro Obs	RR, SP, PP 232 D	≥45 y median 52.8 y	NA	NA	183 platform	6.4 y	Risk of relapse in the 1st year	6% platform, 9% FTY, 43% NTZ
						49 HET	4.2 y		
Corboy et al.[66]	RCT	RR, SP, PP N = 259 128 C / 131D	≥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 *et al.*[67]	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 *et al.*[68]	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 *et al.*[69]	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 *et al.*[70]	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 *et al.*[71]	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 *et al.*[72]	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 *et al.*[73]	Retro Obs	RR, SP N = 498 366 C / 132D	>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 et al.[58]	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.*[74]	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**
Platform therapies				
IFNβ, GA, TRF, DMF/DRF	No	Possible	Not investigated	Not justified
Anti-trafficking therapies				
S1PR agonists	Yes	Not recommended	Tapered withdrawal suggested (not yet supported by strong data)	**Switch options:** 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 **Wash-out period as short as possible** (<2 months and ideally ≤1 month) **Beware of carryover PML**
Natalizumab	Yes	Not recommended	Dosing interval ≤ 6 weeks if JCV status negative (or index < 0.9)	
Anti-CD20 agents	No	Possible	Possible and supported by real word data for rituximab and ocrelizumab (RCTs ongoing) Lack of data for ofatumumab	Switch to platform therapies: possible but limited data
IRT				
Cladribine, Alemtuzumab, AHSCT,	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

AHSCT = 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; S1PR = sphingosine-1-phosphate receptors; TRF = teriflunomide.

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

DMT subtype	Maintenance up to conception *If not, minimum time from last dose*	Maintenance during pregnancy	Bridge therapy	Breastfeeding
IFN β and GA	Yes	Possible, depending on pre-treatment activity	Not necessary	Possible
TRF	No *≥24 months or accelerated elimination procedure (recommended)*	No	Possible if justified	Contraindicated
DMF/DRF	Yes	No Stop when confirmed pregnancy	Not necessary	Not recommended
S1PR modulators	No	No	Strongly recommended **During pregnancy planning period:** Anti-CD20 agents[a]: in priority Cladribine[a], NTZ: may be considered IFN β/GA, DMF/DRF: possible but potentially less effective	Contraindicated
Fingolimod	*≥2 months*			
Ozanimod	*≥3 months*			
Ponesimod	*≥1 week*			
Siponimod	*≥10 days*		**If pregnancy started while on treatment:** depending on pre-treatment activity, NTZ or IFN β/GA can be considered	
Natalizumab	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)	**During pregnancy planning period:** possible *(alternative scenario to maintenance)* Anti-CD20 agents[a]: in priority Cladribine[a]: may be considered IFN β/GA, DMF/DRF: possible but potentially less effective	Possible
			If pregnancy started while on treatment: not recommended, maintain NTZ until 30–34 weeks of gestation	
Anti-CD20 agents				
RTX / OCR	Not recommended *≥2-3 months*	No, unless absolutely needed	Not necessary	Possible
Ofatumumab	Possible	No, unless absolutely needed	Lack of data	
IRTs	No	No	No	Contraindicated during treatment
Cladribine	*≥6 months (women and men), ideally after the 2nd treatment cycle*			Possible ≥1 week after last dose
Alemtuzumab	*≥4 months, ideally after the 2nd treatment cycle*			Possible ≥4 months after last dose
Mitoxantrone	*≥6 months (women and men)*			Possible ≥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; IFNβ = interferon beta; IRTs = immune reconstitution therapies; JCV = John Cunningham virus; NTZ = natalizumab; OCR = ocrelizumab; RTX = rituximab; S1PR = sphingosine-1-phosphate receptors; TRF = teriflunomide.
[a]Conception should be planned according to the respective recommendations for these molecules.

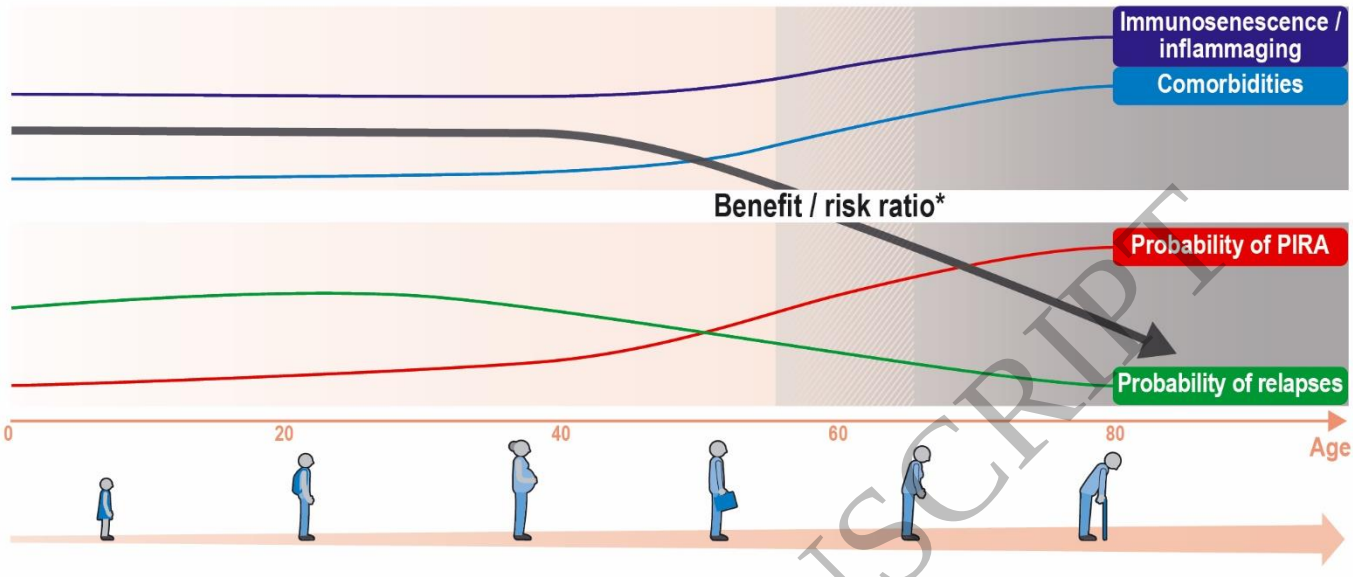

Figure 1
179x77 mm (DPI)

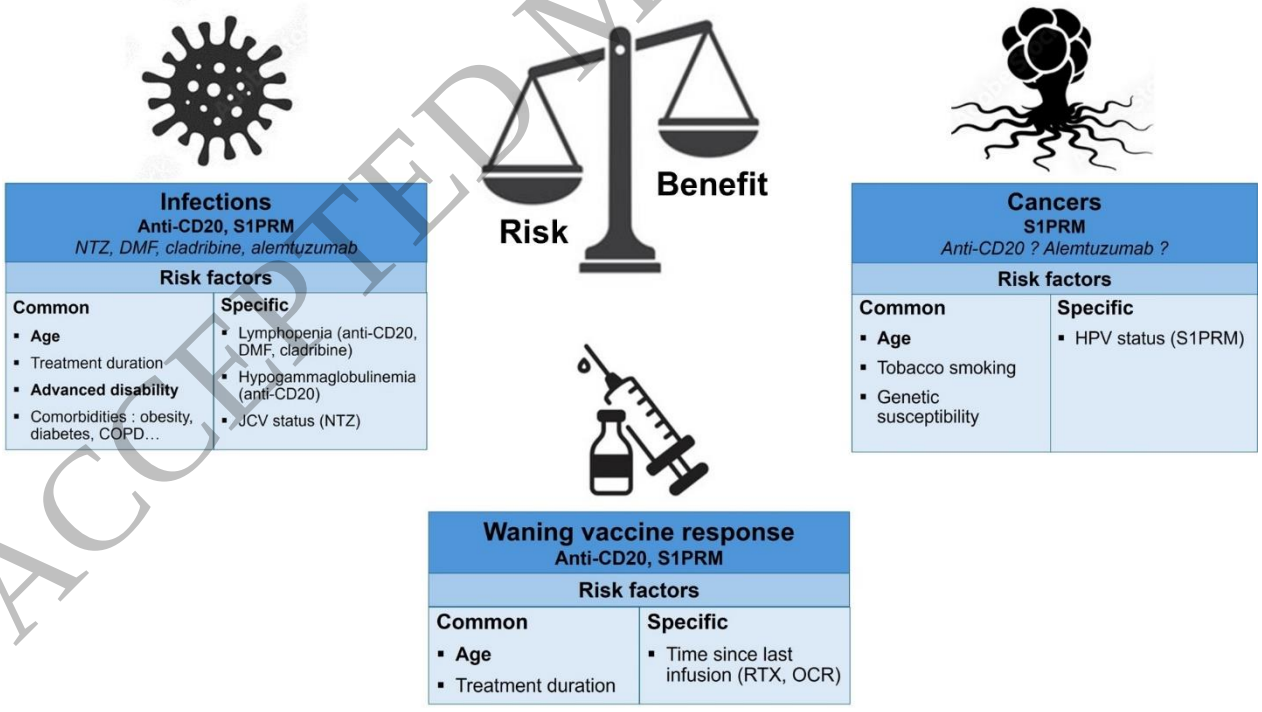

Figure 2
322x187 mm (DPI)

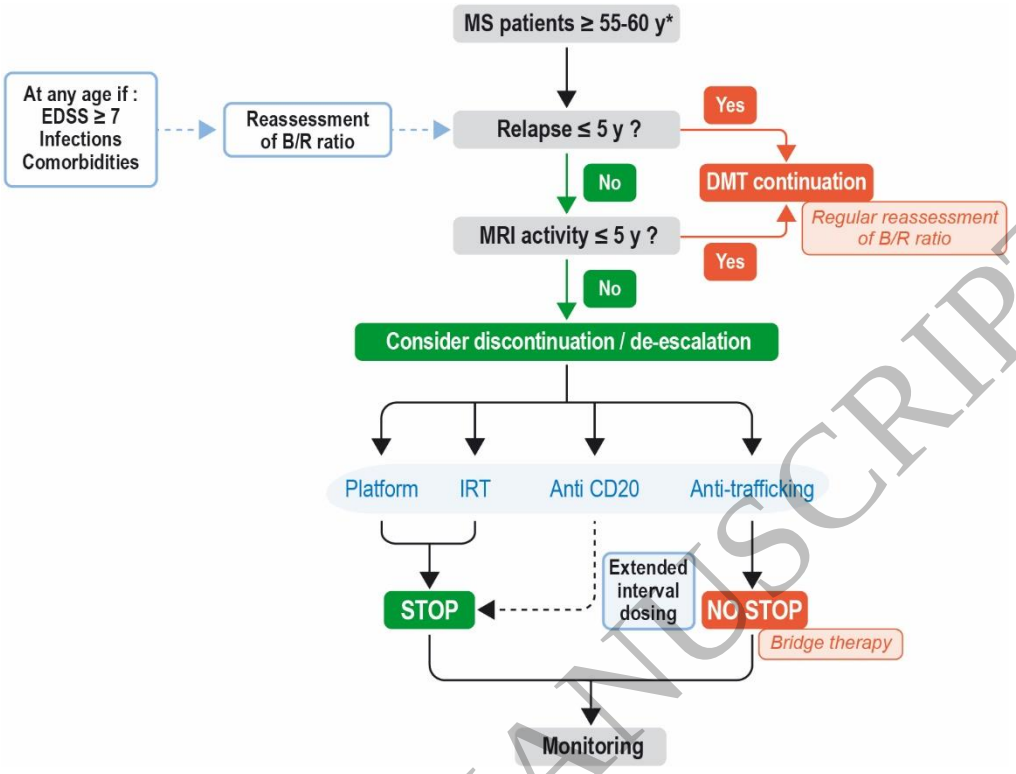

Figure 3
133x101 mm (DPI)

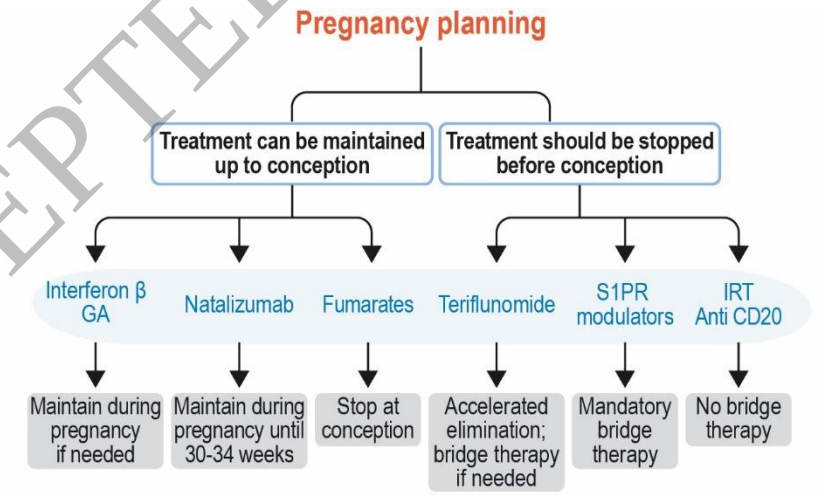

Figure 4
108x65 mm (DPI)