ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Multiple Sclerosis Disease-Modifying Treatment Algorithms: 2025 Positioning of the Portuguese Multiple Sclerosis Study Group

Algoritmos das Terapêuticas Modificadoras da Esclerose Múltipla: Posicionamento do Grupo de Estudos de Esclerose Múltipla em 2025

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Acta Med Port 2025 Jun-Jul;38(6-7):414-426 ▪ https://doi.org/10.20344/amp.22380

ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune-mediated neurodegenerative disease characterized by inflammation, demyelination, and axonal/neuronal damage in the central nervous system. In Portugal, the prevalence of MS is approximately 64.4 per 100 000 individuals. It is typically diagnosed in young adults aged 30 to 40, with a higher incidence in women, although it can also affect children/adolescents and the elderly. Recent advances in MS treatment include the development and approval of several new disease-modifying therapies (DMTs) such as ocrelizumab, cladribine, siponimod, and others, thus expanding options for relapsing-remitting MS (RRMS). However, the options for progressive forms of MS remain limited. In Portugal, MS management strategies, guided by the 2015 recommendations of the Directorate-General of Health and the Portuguese medicines agency, need updating to incorporate recent scientific evidence and clinical expertise. The aim of this manuscript is to highlight gaps in current Portuguese MS treatment algorithms and propose enhancements aligned with global standards, thus improving treatment selection and patient outcomes in the Portuguese healthcare system. Developed by nine Portuguese neurology experts from the Portuguese Multiple Sclerosis Study Group, this document not only provides evidence and clinical practice-based recommendations but also includes DMT algorithms tailored for various MS subtypes, including radiologically and clinically isolated syndromes, RRMS, progressive MS, and specific situations in MS treatment such as pediatric-onset MS, late-onset MS, pregnancy and breastfeeding. This document provides evidence- and clinical practice-based recommendations to optimize decision-making during MS management in Portuguese centers. The experts aim to prompt the urgent revision of national MS treatment frameworks, incorporating the latest advancements in MS research and international guidelines, to reduce the socio-economic burden on the national healthcare system and improve the long-term health outcomes of MS patients.
Keywords: Age of Onset; Multiple Sclerosis/drug therapy; Multiple Sclerosis, Relapsing-Remitting/drug therapy

RESUMO

A esclerose múltipla (EM) é uma doença neurodegenerativa crónica mediada por autoimunidade, caracterizada por inflamação, desmielinização e lesões axonais/neuronais no sistema nervoso central. Em Portugal, a prevalência da EM é de aproximadamente 64,4 por 100 000 indivíduos. A EM é geralmente diagnosticada em adultos jovens entre 30 e 40 anos, com maior incidência nas mulheres, embora também possa ocorrer em crianças/adolescentes e idosos. Avanços recentes no tratamento da EM incluem o desenvolvimento e aprovação de várias novas terapêuticas modificadoras da doença (TMD), como ocrelizumab, cladribina, siponimod e outras, ampliando assim as opções para a EM surto-remissão (EMSR). Contudo, as opções para as formas progressivas de EM permanecem limitadas. Em Portugal, as estratégias de gestão da EM, orientadas pelas recomendações de 2015 da Direção-Geral da Saúde e do Infarmed, carecem de urgente atualização para incorporar evidências científicas recentes e perícia clínica. Este manuscrito tem como objetivo destacar lacunas nos atuais algoritmos de tratamento da EM em Portugal e propor melhorias alinhadas com os padrões globais, melhorando a seleção de terapêuticas e os resultados dos doentes no sistema de saúde português. Desenvolvido por nove especialistas portugueses em neurologia do Grupo de Estudos de Esclerose Múltipla, este documento fornece recomendações baseadas na evidência e na prática clínica, incluindo algoritmos de tratamento com TMD adaptados para vários subtipos de EM, incluindo síndromes clinicamente e radiologicamente isoladas, EMSR, EM progressiva e situações específicas no tratamento da EM, como EM pediátrica, EM de início tardio, e a gestão na gravidez e amamentação. Este documento oferece recomendações baseadas em evidências e práticas clínicas para otimizar a tomada de decisão durante a gestão da EM em centros

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Recebido/*Received*: 01/10/2024 - **Aceite/*Accepted*:** 24/01/2025 - **Publicado *Online*/*Published Online*:** 06/05/2025 - **Publicado/*Published*:** 02/06/2025

portugueses. Os especialistas pretendem incentivar a revisão urgente das normas de tratamento da EM, incorporando os avanços mais recentes na pesquisa sobre a EM e nas diretrizes internacionais, com o intuito de reduzir o impacto socioeconómico no sistema de saúde nacional e melhorar os resultados de saúde de longo prazo dos doentes com EM.
Palavras-chave: Esclerose Múltipla/tratamento farmacológico; Esclerose Múltipla Recidivante-Remitente/tratamento farmacológico; Idade de Início

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune-mediated neurodegenerative disease, characterized by inflammation, demyelination, and axonal/neuronal damage on the central nervous system.[1] In Portugal, it is estimated that 64.4 per 100 000 individuals are affected by MS.[2] This disease is usually diagnosed in young adults of 30 to 40 years of age, has a higher incidence in women than men (3:1), and can be observed during childhood/adolescence (< 18y) or in the senior population (≥ 50y).[3-5]

Diagnosis of MS is based on the McDonald criteria (last revision in 2017),[6] which involves a combination of clinical evaluation, imaging studies [magnetic resonance imaging (MRI)], and laboratory tests [cerebrospinal fluid (CSF)]. Its phenotypes can be categorized as relapsing or progressive in the context of current medical status and history (Table 1), but these categories do not provide temporal information about the ongoing disease process. On this note, the 2013 phenotypic classification update by the US National Multiple Sclerosis Society Advisory Committee on Clinical Trials in Multiple Sclerosis introduced "disease activity" [detected by clinical relapses and/or lesion formation on MRI (T1 gadolinium-enhancing lesions and/or new or enlarging T2 lesions) on an annual timeframe] and "disease progression" (clinical evidence of disease progression, independent of relapses, assessed annually in patients who have a progressive disease course) as meaningful descriptors of relapsing or progressive MS.[7]

Disease progression can manifest as disability dependent on relapses, known as "relapse-associated worsening" (RAW), and/or as disability progression largely independent of relapses, termed "progression independent of relapse activity" (PIRA). Briefly, RAW occurs when relapses directly contribute to the accumulation of disability, while PIRA represents a gradual worsening of disability that occurs without associated relapses, driving the progression of progressive MS.[8] Understanding these concepts is crucial for tailoring treatment strategies to effectively manage both aspects of disease progression in MS.

The revised disease classification, incorporating disease activity (relapses and MRI), has updated the previous terms "progressive relapsing MS" (PRMS) and "secondary progressive MS with relapses" (SPMSr) to "active primary progressive MS" (aPPMS) and "active secondary progressive MS" (aSPMS), respectively. Consequently, the terms "PRMS" and "SPMSr" should be discontinued. Of note, the term "relapsing MS" should not be confused with "RRMS", as it also includes "aSPMS".

The 2013 classification considers disease progression only in progressive forms (PPMS and SPMS), but it is currently consensual that MS is progressive from the onset and, therefore, the axis of progression should also be considered as well in relapsing forms of the disease. While not considered *per se* as a phenotype of MS, radiologically isolated syndrome (RIS) describes asymptomatic individuals exhibiting suggestive MRI clinical features, thus posing an elevated risk of developing MS.[9,10] Identifying the MS phenotype is crucial to guide treatment decisions and understand the disease course and prognosis for each individual/patient.

Although the course of MS can be extremely heterogeneous and difficult to predict, several prognostic factors have been identified as indicating a higher probability of poor disease outcomes,[11-14] thus being crucial for treatment decisions and for decisions related to various aspects of the patients' life (e.g., family planning, pregnancy, relationships, and work life). The presence of poor prognostic factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], especially when multiple co-existing factors are present, is more likely to result in higher and more frequent disease activity and earlier disability.

The goal of MS disease-modifying therapy (DMTs) is to reduce early clinical and subclinical disease activity, attenuating the accrual of long-term disability.[15-17] To improve long-term patient outcomes and preserve quality of life, it is critical to achieve a sustained state of "no evidence of disease activity-3" (NEDA-3), which encompasses the prevention of

Table 1 – Current MS phenotype classification

Clinically Isolated Syndrome (CIS) **Relapsing-Remitting MS (RRMS)**	Active or Not active
Secondary Progressive MS (SPMS) **Primary Progressive MS (PPMS)**	Active with/without progression or Not active with/without progression

MS: multiple sclerosis

relapses, the halting of disability progression, and the minimization of new/enlarging T2 lesions and/or T1 gadolinium-enhancing lesions on MRI scans.[18]

The armamentarium for MS treatment, summarized in [Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], has expanded very rapidly for RRMS, but remains limited for progressive MS. Over the past 10 years, notable developments have occurred in the field, including the approval of several new DMTs such as ocrelizumab, cladribine, siponimod, ozanimod, ponesimod, ofatumumab and ublituximab. Noteworthy, recent evidence suggests the potential effectiveness of pharmacotherapy in RIS.[19-22] Considering the 2024 McDonald criteria, which had not yet been published at the time of writing this manuscript but were presented at the 2024 European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) conference, RIS may fulfill the criteria for RRMS, and, therefore, may become a potential target for DMTs already approved for RRMS. New molecules are currently under development and have shown promising clinical benefits in MS treatment, such as Bruton's tyrosine kinase (BTK) inhibitors [e.g., tolebrutinib for inactive secondary progressive MS – HERCULES study (NCT04411641)] and CD40L inhibitors (e.g., frexalimab for relapsing MS).[23,24] Additionally, there have been updates to diagnostic criteria, emerging evidence supporting early treatment with high-efficacy DMTs (HE-DMTs), a heightened emphasis on tools for assessing patients' perception of the disease through patient-reported outcomes (PROs), and endeavors to integrate remote monitoring tools used in clinical trials into routine clinical practice. Mitoxantrone, a chemotherapeutic agent previously used in the treatment of aggressive MS, has seen its use significantly restricted due to concerns regarding its potential for severe cardiotoxicity.[25]

In Portugal, current MS management strategies have been guided a decade ago by the 2015 recommendations of Direção-Geral da Saúde (DGS) and by the National Medicines Agency (Infarmed)'s guidance documents – which lack the consideration of the patient's poor prognosis factors in the choice of the treatment algorithm.[26,27]

As the diagnostic criteria for MS continue to evolve and new therapeutic strategies emerge it is evident that the existing treatment recommendations followed by Portuguese centers require revision and updating, drawn upon up-to-date scientific evidence and clinical expertise. This manuscript endeavors to analyze the gaps in the current Portuguese MS treatment algorithms compared to global standards, highlighting the urgency for an updated decision-making framework in Portugal. Drawing from contemporary MS research and the clinical insights of Portuguese experts, this initiative seeks to enhance treatment guidelines tailored to diverse subsets of MS patients within the Portuguese healthcare system, to ultimately provide safe and efficient selection of MS therapies and optimization of patient outcomes.

MATERIAL AND METHODS

Acknowledging the developments and needs on the field, nine Portuguese neurologists with extensive expertise on MS, members of the Portuguese Multiple Sclerosis Study Group (GEEM), endorsed a series of expert meetings to draw a consensus document advocating for revision of the current MS treatment framework in Portuguese centers. The goal of this document is to aid decision-making for MS specialists, to help reduce excessive variation in practice, and ensure safe and effective prescribing. The proposed MS treatment algorithms presented herein reflect the consensus opinions of all authors based on their clinical experience, and are built upon the currently available guidelines from the ECTRIMS/European Academy of Neurology (EAN) guidelines for Europe, the Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS) for the Middle East/North Africa, the American Academy of Neurology (AAN) for North America, and the individual initiatives of the Multiple Sclerosis Therapy Consensus Group (MSTCG), the National Institute for Health and Care Excellence (NICE) and the Spanish Society of Neurology.[28-33]

The experts' recommendations for the management of MS in Portugal

The panel of expert neurologists from GEEM convened to develop various algorithms to guide the therapeutic strategies for MS, including specific situations such as pediatric onset MS, MS management during pregnancy and breastfeeding, and late-onset MS, based on the available scientific evidence, approved indication labels, and expert opinion.

Choosing the best treatment strategy: escalation or early initiation of HE-DMTs

The classification of DMTs based on efficacy lacks uniformity in the literature, particularly regarding the inconsistent positioning of S1P receptor modulators and cladribine. Given this, the GEEM experts collectively decided to introduce a third efficacy category, "low efficacy," to complement the commonly used "moderate efficacy" and "high efficacy" classifications. Accordingly: i) low efficacy DMTs include IFNβ formulations, glatiramer acetate, teriflunomide, and dimethyl fumarate; ii) moderate efficacy DMTs include S1P receptor modulators (fingolimod, ozanimod, ponesimod, siponimod) and cladribine; and iii) high efficacy DMTs comprise monoclonal antibodies, specifically natalizumab, alemtuzumab, and anti-CD20 therapies (ocrelizumab,

ofatumumab, and ublituximab).

The decision to initiate DMTs for MS is based on several factors, which include the patient's disease characteristics (e.g., clinical presentation, frequency of relapses, MRI findings, and disability progression), prognostic factors, and patient-neurologist shared decision making. Immunomodulatory/immunossupressive DMTs should be offered as soon as possible to control disease activity and progression to i) patients with RIS with persistent imaging activity; ii) patients with CIS and risk of progression to MS; iii) RRMS; iv) aSPMS; v) aPPMS; vi) younger patients (≤ 50) with inactive SPMS (iSPMS) and PPMS (iPPMS) with progression.

The prevailing guidelines in Portugal endorse an escalation approach, initiating patients with low- and moderate-efficacy DMTs (LE-/ME-DMTs, respectively) and transitioning to HE-DMTs, if increased disease activity, poor compliance or side effects are observed.[26,34] Opting for such a conservative management approach may have limitations in terms of disease control and long-term outcomes. The rationale for initiating early HE-DMTs to mitigate disease progression in the initial stages of MS is supported by an increasing body of evidence consistently demonstrating that early start of HE-DMTs, as opposed to LE-/ME-DMTs or early transitioning to HE-DMTs, may yield optimal benefits in managing the evolution of MS.[35-42] This is attributed to their heightened capacity to curtail the accumulation of irreversible clinical disability, the onset of secondary progressive MS, and the advancement of brain atrophy more effectively. This approach is particularly relevant for patients with aggressive forms of MS or those who have failed to respond adequately to LE-/ME-DMTs. However, one should keep in mind that this approach requires careful monitoring and management.

Controlled trials directly comparing escalation treatment and early onset of HE-DMTs are lacking. However, observational studies and subgroup analyses from clinical trials consistently suggest that patients receiving early HE-DMTs treatment exhibit less disease activity, reduced disability, and a lower risk of progressing to SPMS within the first five years compared to those receiving these treatments later.[37,39,43,44] Real-life studies indicate that patients treated early with HE-DMTs are approximately twice as likely to achieve NEDA-3 compared to those treated with LE-/ME-DMTs.[45] Considering that persistent clinical or subclinical activity may lead to irreversible neurological damage, it is reasonable to consider HE-DMTs as the initial option after weighing the risks and benefits of treatment.

Proposed treatment algorithms for MS

The initial treatment decision in MS should be based on shared decision-making between the clinician and patient, taking into account both patient-related factors and drug-related factors. Choosing a specific drug involves considering not only patient prognostic factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], and drug-related factors, but also individual patient factors such as age, sex, literacy, occupation, family planning, comorbidities, disease phenotype, type of deficits, progression of disability, disease activity, autonomy/dependence, presence of cognitive deficits, comfort, expectations, concerns, and motivation for effective adherence to prescribed medication.[11] This comprehensive approach ensures that the chosen therapy aligns with the patient's unique circumstances, leading to more effective and satisfactory outcomes.

Radiologically isolated syndrome

Patients diagnosed with radiologically isolated syndrome (RIS) should be promptly referred to a specialized MS center for monitoring. If multiple risk factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)] are present and follow-up MRI reveals evidence of new lesions, treatment should be initiated (teriflunomide or dimethyl fumarate) (Fig. 1).[21,22] Under the updated 2024 McDonald diagnostic criteria (not yet published at the time of manuscript preparation), RIS may meet the criteria for relapsing-remitting multiple sclerosis (RRMS), making it eligible for DMTs approved for RRMS.

Clinically isolated syndrome

Clinically isolated syndrome (CIS) patients who do not fulfill the criteria for MS and present abnormal MRI findings (≧ 2 T2 lesions), thus being considered high-risk,[46] should be treated with IFNβ formulations, glatiramer acetate, teriflunomide or cladribine (Fig. 1). In the presence of one or two poor prognostic factors, cladribine should be considered.[47,48]

Relapsing-remitting multiple sclerosis

Upon disease activity detection on treatment-naïve patients with i) zero unfavorable prognostic factors, one should consider LE-DMTs as IFNβ, glatiramer acetate, teriflunomide or dimethyl fumarate; ii) one to two unfavorable prognostic factors, one should consider ME-DMTs as S1P receptor modulators and cladribine; or iii) more than two unfavorable prognostic factors, one should consider HE-DMTs as natalizumab, anti-CD20/B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, ublituximab), and alemtuzumab (Fig. 1). Patient-related factors should also be considered for the choice of DMT [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)].

The treatment strategy for patients on DMTs should be

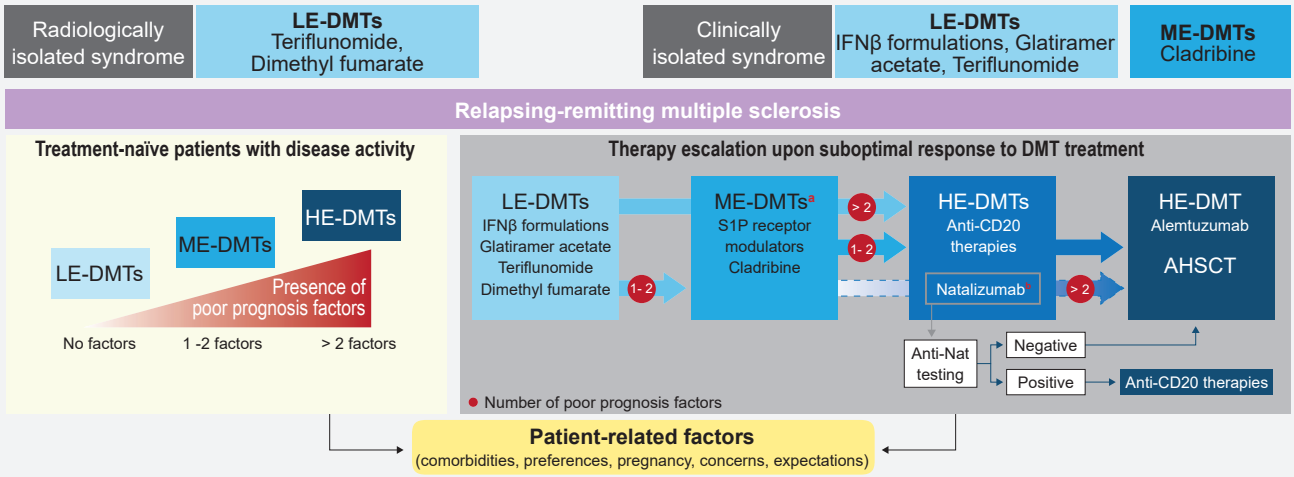

Figure 1 – 2025 algorithm for the management of RIS, CIS and RRMS

Disease activity or suboptimal response is generally defined as "presence of relapses, new/enlarged T2 lesions, gadolinium-enhancing T1 lesions, or confirmed disability progression over one year (≥ 1.5 if EDSS 0; 1.0 if EDSS 1.0 - 5.5; or 0.5 if EDSS ≥ 6.0, sustained across ≥ 2 consecutive visits separated by ≥ 6 months). In both treatment-naïve patients and those with a suboptimal response to DMTs, therapeutic switching should take into account the presence of prognostic factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)] and patient-related factors.

a: In case of suboptimal response to ME-DMTs, escalation to HE-DMTs (anti-CD20 therapies or natalizumab) is recommended prior to considering alemtuzumab or AHSCT.

b: In case of suboptimal response to ME-DMTs, natalizumab should be used preferentially in patients with negative JC virus serology. In cases of suboptimal response or infusion reactions before subsequent infusions, the presence of persistent anti-natalizumab antibodies should be confirmed. If positive, a switch to anti-CD20 therapies can be considered. If negative, alemtuzumab or AHSCT may be considered.

AHSCT: autologous hematopoietic stem-cell transplantation; CIS: clinically isolated syndrome; DMTs: disease-modifying therapies; HE-DMTs: high efficacy DMTs; IFNβ: interferon β; LE-DMTs: low efficacy DMTs; ME-DMTs: medium efficacy DMTs; RIS: radiologically isolated syndrome; RRMS: relapsing-remitting multiple sclerosis

carefully reassessed if suboptimal response is detected (Fig. 1). Disease activity or suboptimal response is generally defined as "presence of relapses, new/enlarged T2 lesions, gadolinium-enhancing T1 lesions, or confirmed disability progression over one year (≥ 1.5 if EDSS 0; 1.0 if EDSS 1.0 - 5.5; or 0.5 if EDSS ≥ 6.0, sustained across ≥ 2 consecutive visits separated by ≥ 6 months).[29] Such scenario should prompt a therapeutic switch, in a form of DMT treatment escalation, guided by the presence of poor prognosis factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)] and patient-related factors. In cases where only increased disability is observed during a one-year period of DMT use, DMTs with a stronger impact on this component (PIRA), such as anti-CD20 therapies, should be prioritized.

For patients with suboptimal responses to LE-DMTs (Fig. 1), escalation to ME- or HE-DMTs with an acceptable safety profile should be considered. Suitable options include cladribine, S1P receptor modulators, anti-CD20 therapies or natalizumab for John Cunningham virus (JCV) seronegative patients. Escalation to ME-DMTs is recommended in the presence of one to two poor prognosis factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], whereas escalation to HE-DMTs is advised when more than two poor prognosis factors are present. In such cases, HE-DMTs such as anti-CD20 therapies or natalizumab should be prioritized before considering alemtuzumab or AHSCT.

If suboptimal response/disease activity is observed with ME-DMTs (Fig. 1), escalation to HE-DMTs is recommended. In the presence of one to two poor prognosis factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)], preferred options include anti-CD20 therapies or natalizumab for JCV seronegative patients. Alemtuzumab may be considered, particularly when more than two poor prognosis factors are present.[48-50] Autologous hematopoietic stem-cell transplantation (AHSCT) is also a viable strategy for managing MS refractory to DMT treatment, but should be carefully considered due to the risks of immunosuppression and potential side effects.[51]

For patients with suboptimal responses to HE-DMTs (such as natalizumab, anti-CD20 therapies, including off-label use of rituximab) (Fig. 1), alemtuzumab or AHSCT should be considered. Additionally, in these cases, natalizumab antibody testing should be performed and confirmed in patients who experience infusion reactions or breakthrough disease activity while using natalizumab. If positive, a lateral switch to an anti-CD20 therapy may be appropriate; if negative, a vertical switch to alemtuzumab or AHSCT can be considered.

Active secondary progressive MS and active primary progressive MS

For the treatment of aSPMS (Fig. 2), the following DMTs

can be considered: IFNβ formulations, glatiramer acetate, cladribine, siponimod, ponesimod, ocrelizumab, ofatumumab, and ublituximab. However, the DMTs with the most documented clinical benefit for this form of MS are siponimod and B-cell depleting therapies.[49,50] Since the treatment target is disease activity (inflammation), the same considerations for RRMS should be applied in aSPMS, including the presence of poor prognostic factors and previously employed DMTs.

Ocrelizumab is the only approved therapeutic agent for aPPMS.[50] Ocrelizumab serum levels have been associated with a greater reduction in the risk of disability progression, forming the basis for the ongoing GAVOTTE (NCT04548999; in aPPMS patients) and MUSETTE (NCT04544436; in aSPMS patients) trials.[52] In this context, and given the limited therapeutic options for aPPMS, in cases of disease progression under the standard 600 mg dose of ocrelizumab, higher doses of 1.200 mg in patients < 75 kg or 1.800 mg in patients ≥ 75 kg, every 24 weeks, may be considered (Fig. 2).

Results of a randomized double-blind placebo-controlled multicenter trial (OLYMPUS) suggest that off-label use of rituximab may be also effective in PPMS patients.[51]

Inactive secondary progressive MS (iSPMS) and inactive primary progressive MS (iPPMS)

For the treatment of iSPMS and iPPMS (Fig. 2), specific therapeutic options are considered based on patient age and disease progression. In younger patients (≤ 50 years old) with iSPMS characterized solely by progression, siponimod and anti-CD20 therapies, such as ocrelizumab and ofatumumab, can be considered. Similarly, for ≤ 50 year old patients with iPPMS showing only progression, ocrelizumab, potentially at higher doses, is a viable treatment option. These treatments focus on managing disease progression in the absence of active inflammation.

Therapeutic switch

Upon the decision to switch DMTs (Figs. 1, 2), a washout period is typically implemented before starting the second DMT, to mitigate the potential risks associated with cumulative effects (Table 2). Therefore, the switching process poses challenges for patients that should be considered: i) a brief washout period between DMTs heightens the likelihood of adverse events (e.g., opportunistic infections due to DMT-induced immunosuppression), and ii) an extended washout period raises the risk of reactivation/rebound disease activity, including relapses, worsening disability, and/or increased MRI activity. Therapeutic switch should be performed under the following principles:

- If discontinuing LE-DMTs, another LE-DMTs or ME/HE-DMTs or an induction therapy may be initiated without a washout period, provided the patient's biological test results are normal.
- In both treatment-naïve patients and those with a suboptimal response to DMTs (Fig. 1), therapeutic switching should take into account the presence of prognosis factors [Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22380/15663)] and patient-related factors.
- Clinicians should consider the transition to non-injectable or less frequently injectable DMTs if patients report discomfort with injections or exhibit signs of

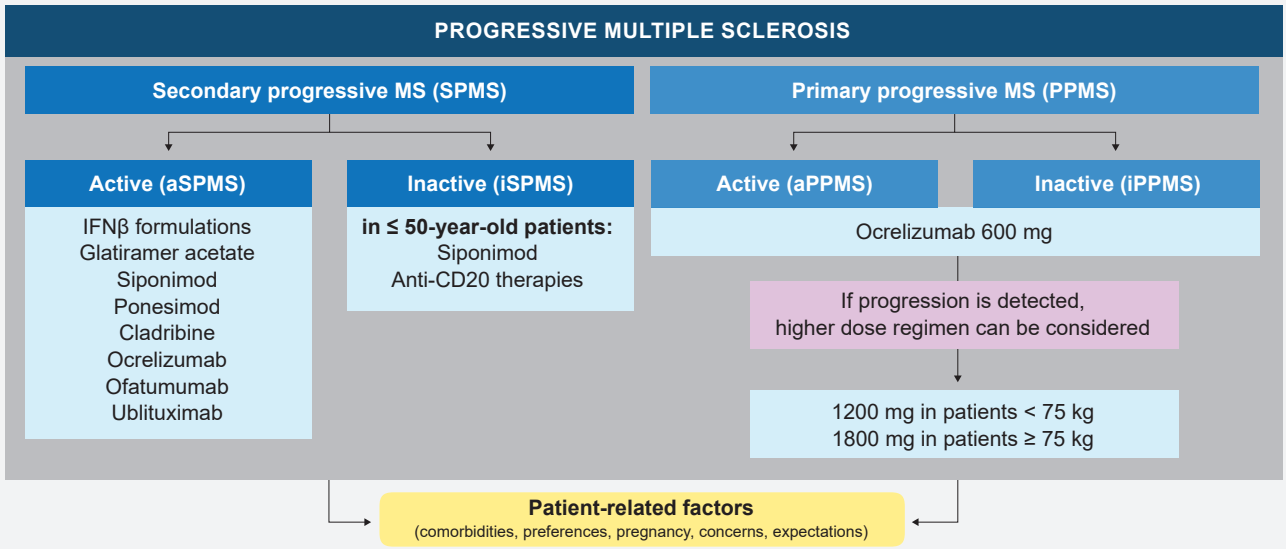

Figure 2 – 2025 algorithm for the management of progressive MS
IFNβ: interferon β; MS: multiple sclerosis; PPMS: primary progressive MS; SPMS: secondary progressive MS

Table 2 – Recommended washout periods after disease-modifying therapies switch

Discontinued DMT	Washout time before starting LE-DMT	Washout time before starting ME/HE-DMT or induction therapy
IFNβ	No washout	No washout
Glatiramer acetate	No washout	No washout
Teriflunomide	No washout	No washout
Dimethyl fumarate	No washout (if lymphocyte count > 800/mm^3)	No washout (if lymphocyte count > 800/mm^3)
Fingolimod		One month
Siponimod		10 days
Ozanimod		One month
Ponesimod		One week
Natalizumab		One month
Alemtuzumab		If disease activity (clinical or imaging)
Ocrelizumab		Six months (or until B-cell repletion)*
Ofatumumab		One month (or until B-cell repletion)*
Ublituximab		Six months (or until B-cell repletion)*
Cladribine		If disease activity (clinical or imaging)

*: The therapeutic switch can coincide with the scheduled infusion (ocrelizumab and ublituximab: every six-months infusion; ofatumumab: every one-month infusion).
DMT: disease-modifying therapy; HE-DMT: high efficacy DMT; IFN: interferon; LE-DMT: low efficacy DMT; ME-DMT: medium efficacy DMT.

injection fatigue.

- Clinicians should discuss a switch to a DMT with a lower risk of progressive multifocal leukoencephalopathy (PML) in patients under natalizumab and anti-JCV seropositive (particularly if their anti-JCV antibody index rises above 0.9 while on therapy).
- A one-month washout period is typically recommended when switching from S1P receptor modulators to anti-CD20 therapies and natalizumab, although this may vary depending on the specific S1P receptor modulator used. However, disease reactivation is common after discontinuing S1P receptor modulators, requiring close monitoring. The preference for anti-CD20 agents after S1P receptor modulators is due to their rapid B-cell depleting effect, with onset times ranging from 24 hours for ublituximab to 14 days for ocrelizumab and ofatumumab.
- In cases of switching to cladribine, caution is required due to its delayed onset of action, which may increase the risk of disease reactivation or rebound.[53] Therefore, a bridging strategy with an anti-CD20 agent should be considered. Given this, particularly in the context of switching from S1P receptor modulators during pregnancy, cladribine should be avoided in favor of natalizumab or anti-CD20 therapies, which are more appropriate options in this setting.
- When determining the required washout period from anti-CD20 therapies for a therapeutic switch in MS treatment, the duration depends on the speed of B-cell reconstitution, which varies among anti-CD20 therapies. For example, median time to B-cell repletion for ocrelizumab is 72 weeks, 24.6 weeks for ofatumumab, and 70 weeks for ublituximab.

Specific situations in MS treatment

Pediatric onset MS

Pediatric onset MS (POMS) is generally defined as MS with onset before the age of 18 years, and 3% - 10% of all MS patients have their first demyelinating attack before the age of 16 years.[54] In agreement, two studies conducted in Portugal found that 9.2% of MS patients had symptoms starting at a young age, and the average age of initial symptom onset was 14 years.[55,56] The 2017 revised McDonald criteria for adult-onset MS are widely used as diagnostic criteria for the pediatric population.

Early intervention is crucial in POMS, as these patients reach irreversible disability at a younger age than patients with adult-onset MS,[57] and 98% of the pediatric patients present a relapsing-remitting course.[58] Given the relatively high relapse rate and accumulation of disability at younger age, early initiation of DMTs is recommended to reduce the intense inflammatory process early in the disease.[59] Several DMTs are currently used for the management of POMS, which have proved useful and safe approaches due to their high tolerance and effective reduction of relapse rate and disease activity, as well as long market experience (Table 3). These include injectable therapies, such as IFNβ-1a/-1b and glatiramer acetate.[60-65] Oral therapies such as teriflunomide, fingolimod, dimethyl fumarate or monoclonal

Table 3 – Overview of the disease-modifying therapies for POMS. The information is based on the EMA Summary of Product Characteristics (SmPC) for each medication

DMTs	EMA approved indication (SmPC)
IFN-βa*	Children > 10 years: • IFN-β-1a: IM 30 mcg, once weekly • IFN-β-1a: SC 22 mcg or 44 mcg, three times weekly • IFN-β-1b: SC 8250 mcg, every other day
Glatiramer acetate*	Children > 10 years: • SC 20 mg daily • SC 40 mg three times per week
Fingolimod	• ≤ 40 kg bodyweight: oral 0.25 mg, daily • > 40 kg bodyweight: oral 0.5 mg, daily
Teriflunomide	• ≤ 40 kg bodyweight: oral 7 mg, daily • > 40 kg bodyweight: oral 14 mg, daily
Azathioprine*	Oral 2 - 3 mg/kg daily
Cyclophosphamide*	600 to 1.000 mg/m^2 per dose - Induction regimen of 5 doses provided over 8 days followed by monthly pulse treatments or single induction course of 5 doses over 8 days or monthly without induction
Dimethyl fumarate	Oral 120 mg BID for 7 days, then 240 mg BID
Rituximab*	IV 750 mg/m^2 (500 – 1.000 mg) every 6 months, induction with 2 doses separated by 2 weeks
Natalizumab*	IV 300 mg, every 4 weeks

*: off-label use
BID: bidaily; EMA: European Medicines Agency; IFN: interferon; IM: intramuscular; IV: intravenous; POMS: pediatric onset multiple sclerosis; SC: subcutaneous.

antibodies have also shown promise in POMS, offering dosing convenience and a better adherence.[66-70] Of these, only fingolimod (for patients aged 10 years or older), teriflunomide (for patients aged 10 - 17 years) and dimethyl fumarate (for patients aged 13 - 17 years) have formal approval from the European Medicines Agency. The use of azathioprine and cyclophosphamide in POMS is both off-label and highly exceptional, reserved only for cases of extreme clinical or radiological aggressiveness where no response to other treatments is observed, or when other drugs are contraindicated. Rituximab, although also off-label in POMS, may present a more practical option and is currently under investigation alongside ocrelizumab and ofatumumab, whose efficacy and safety are being actively studied in the pediatric MS population.[71] Natalizumab was also shown to have consistent effectiveness in reducing disease activity in pediatric patients, including children with aggressive disease onset.[72,73] To safeguard the risk-benefit of natalizumab use on pediatric patients, given the associated risk of PML, regular serologic testing for anti-JCV antibodies and MRI screening are crucial.[73-75]

Clinicians managing pediatric patients with MS face the challenging decision of whether to commence treatment with a safer, yet potentially less effective, injectable therapy and escalate if insufficient response is observed, or to initiate a more potent treatment despite its less favorable safety profile, underscoring the need for personalized treatment strategies. Close monitoring is essential to detect potential complications or treatment ineffectiveness, ensuring optimal outcomes for children with MS. Although a significant portion of the DMTs employed in this population remains off-label, ongoing clinical trials are exploring additional options, such as siponimod (NCT04926818), ofatumumab (NCT04926818) and ocrelizumab (NCT04075266, NCT05123703) and, in the short-term, ponesimod and ozanimod. Globally, these studies are expected to catalyze further research and, eventually, faster approval by regulatory bodies.

Late-onset MS

Late-onset MS (LOMS) is conventionally defined when MS manifests at ≥ 50 years, with a prevalence rate ranging from 0.6% to 12%.[76,77] Accounting for ≈5% of total MS cases, LOMS has motor involvement as the most common clinical phenotype, in contrast to early onset-MS.[78] Moreover, LOMS is associated with higher EDSS when considering the same disease duration, translating into increased disability.[79] The prevalence of progressive forms in LOMS poses challenges in terms of selecting appropriate treatments, and age is considered an essential modifier of DMTs efficacy in MS patients.[80] Despite these limitations, DMTs are often prescribed to LOMS patients, although evidence regarding their safety and efficacy is scarce.[49,81-86]

Pregnancy and breastfeeding

Managing MS during pregnancy and breastfeeding poses unique challenges for women of childbearing age. The fluctuating hormonal levels during pregnancy may influence

the course of the disease, leading to symptom improvement or worsening. Nonetheless, MS does not appear to carry a significant risk for an adverse pregnancy outcome compared with women without MS.[87,88]

While all DMTs carry the potential for adverse effects on the fetus, the universal recommendation is to cease treatment prior to attempting conception. Nevertheless, this strategy heightens the risk of relapse, particularly if conception is delayed. Moreover, there are concerns regarding the potential hazards associated with discontinuing beneficial DMTs during pregnancy, especially in women with highly active disease.

Guidelines for the management and treatment of MS during pregnancy and breastfeeding (Table 4) have been delineated in a previous publication by experts from GEEM.[89] Overall, we recommend:

- A thorough analysis of the DMTs risk profile (including risks of fetal exposure pre-conception and during pregnancy), and factors associated with a high risk of postpartum activity (severity of the disease in previous years, number of relapses, accumulated disability, or lesion burden) should be performed.
- Disease activity should be determined through regular clinical assessment, at least every three months.
- Routine MRI monitoring for lesion burden should be avoided during pregnancy, thus being reserved only if essential for therapeutic decision-making and gadolinium should not be administered.
- Glatiramer acetate and IFNβ are currently accepted as safe therapies during pregnancy.
- Natalizumab treatment should be continued until 34 weeks of gestation for women, expanding interval

Table 4 – Guidance for use of approved DMTs for MS during pregnancy and breastfeeding[97]

DMTs	Preconception washout	During pregnancy	During breastfeeding
IFNβ	Not necessary	Acceptable	Acceptable (evaluate risk-benefit)
Glatiramer acetate	Not necessary	Acceptable	Possibly acceptable (evaluate risk-benefit)
Teriflunomide	Discontinuation before conception (accelerated elimination procedure and maintain contraception until plasma levels of teriflunomide are < 0.02 mg/L)	Contraindicated*	Contraindicated
Dimethyl fumarate	Stop when pregnancy confirmed	Not recommended	Not recommended
Natalizumab	Maintain during conception	Maintain during pregnancy up to 34 weeks; resume 1-2 weeks post-partum	Acceptable
Alemtuzumab	Discontinuation before conception; maintain contraception for four months	Not recommended	Acceptable
Ofatumumab	Stop when pregnancy confirmed (time monthly injection with menses to decrease chance of exposure in pregnancy)	Not recommended	Acceptable
Ocrelizumab	Discontinuation before conception; maintain contraception for two months	Not recommended	Acceptable
Rituximab	Discontinuation before conception; maintain contraception for two months	Not recommended	Acceptable
Ublituximab	Discontinuation before conception; maintain contraception for four months	Not recommended	Acceptable
Cladribine	Discontinuation before conception; maintain contraception for six months	Not recommended	Contraindicated
Fingolimod	Discontinuation before conception; maintain contraception for two months	Not recommended	Not recommended
Ozanimod	Discontinuation before conception; maintain contraception for three months	Not recommended	Contraindicated
Siponimod	Discontinuation before conception; maintain contraception for 10 days	Not recommended	Contraindicated
Ponesimod	Discontinuation before conception; maintain contraception for one week	Not recommended	Contraindicated

*: due to possible teratogenicity.
DMTs: disease-modifying therapy; IFN: interferon; MS: multiple sclerosis.

dosing to six weeks, and to resume the treatment one to two weeks postpartum.[90-92]

- Fingolimod, siponimod, ozanimod, ponesimod, teriflunomide, cladribine, ocrelizumab, ofatumumab, ublituximab, and alemtuzumab should not be used during pregnancy, and should be discontinued before conception, with washout periods adapted according to their respective half-lives.
- Regarding S1P receptor modulator discontinuation, due to the risk of disease reactivation and rebound, a switch to natalizumab or anti-CD20 agent is recommended before pregnancy.
- Only IFNβ, glatiramer acetate, ofatumumab and ublituximab are approved for use during breastfeeding.
- Breastfeeding should be avoided in patients on teriflunomide, S1P receptor modulators, dimethyl fumarate and cladribine. In general, monoclonal antibodies (alemtuzumab, natalizumab, rituximab, ocrelizumab, ofatumumab, ublituximab) are secreted in negligible amounts in breastmilk two-weeks postdelivery (skipping the initial secretion of colostrum), due to its large molecular weight. Therefore, all aforementioned medicines can be considered safe for use during breastfeeding.

Monitoring of treatment effectiveness and follow-up

The effectiveness of DMTs should be regularly evaluated through periodical clinical assessments as well as MRI scans to detect new or enlarging brain lesions, which are a sign of active inflammation and disease activity. For monitoring and follow-up, we recommend following the Spanish Society of Neurology guidelines[33]:

- Follow-up consultations should occur every three months following the initiation of the first DMTs. However, visit frequency should be tailored to individual patient characteristics and treatment responses.
- Regardless of the chosen DMTs (LE, ME or HE), follow-up consultations should be conducted at least every six months for patients who are clinically and radiologically stable, and every three months for unstable patients whenever feasible. If progression to SPMS is suspected, follow-up consultations should be scheduled at least every six months.
- MRI study should be performed three to six months after DMTs onset to serve as a new reference point (re-baseline) and annually thereafter.

Patient-reported outcome measures (PROM) and patient-reported experience measures (PREM) are also valuable tools to assess the impact of DMTs' on activities of daily living, to guide treatment decisions and monitor long-term treatment [e.g., Multiple Sclerosis Impact Scale (MSIS-29), Modified Fatigue Impact Scale, Multiple Sclerosis International Quality of Life questionnaire (MSQOL)].[93] Biomarkers (e.g., loss of brain or spinal cord volume on MRI or CSF-specific biomarkers as IgG and/or IgM oligoclonal bands, serum biomarkers as glial fibrillary acid protein (GFAP) and NfL levels) are also promising tools for prediction of disease progression and evaluation of treatment response.[94-96]

CONCLUSION

This document developed by Portuguese neurology experts from GEEM provides evidence and clinical practice-based recommendations intended to optimize the management of MS in Portuguese centers. With this effort, the experts aim to prompt the urgent revision of national MS treatment frameworks, reflecting the latest advancements in MS research and international guidelines, thus reducing the socioeconomical burden on the national healthcare system and improving the long-term health outcomes of MS patients.

ACKNOWLEDGMENTS

Editorial support in the form of medical writing and editing assistance for manuscript preparation was provided by Evidenze Portugal.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This article was fully supported by the Portuguese Multiple Sclerosis Study Group (GEEM), without any additional external funding.

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