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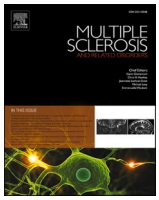

Review article

Consensus recommendations for diagnosis and treatment of Multiple Sclerosis: 2023 revision of the MENACTRIMS guidelines

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ABSTRACT

With evolving diagnostic criteria and the advent of new oral and parenteral therapies for Multiple Sclerosis (MS), most current diagnostic and treatment algorithms need revision and updating. The diagnosis of MS relies on incorporating clinical and paraclinical findings to prove dissemination in space and time and exclude alternative diseases that can explain the findings at hand. The differential diagnostic workup should be guided by clinical and laboratory red flags to avoid unnecessary tests. Appropriate selection of MS therapies is critical to maximize patient benefit. The current guidelines review the current diagnostic criteria for MS and the scientific evidence supporting treatment of acute relapses, radiologically isolated syndrome, clinically isolated syndrome, relapsing remitting MS, progressive MS, pediatric cases and pregnant women. The purpose of these guidelines is to provide practical recommendations and algorithms for the diagnosis and treatment of MS based on current scientific evidence and clinical experience.

1. Background

Multiple Sclerosis (MS) is a chronic demyelinating disorder of the central nervous system (CNS) that affects predominately patients aged 20–40 years. The epidemiology of MS is changing worldwide, as is the understanding of its immunopathogenesis and natural history, with new

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evidence pointing towards a multifactorial etiology involving both environmental and genetic factors (Goodin, 2014; Trojano et al., 2011). The prevalence and incidence rates of MS have been steadily increasing worldwide over the last few decades including the Middle East North Africa (MENA) region (El-Salem et al., 2006; Al-Hashel et al., 2008; Inshasi and Thakre, 2011; Deleu et al., 2013; Alroughani et al., 2014; Etemadifar et al., 2014). The field of MS therapeutics is evolving rapidly as several novel disease modifying therapies (DMTs) have been added to our armamentarium in the last decade. There is a clear need to unify and update the diagnostic and therapeutic paradigms across the MENA region as most countries in the region are in the process of establishing specialized MS centers. On the other hand, some diagnostic mimickers of MS, such as neurobrucellosis, neuro-Behçet, Toxocara canis myelitis (Jabbour et al., 2011), Human T-lymphotropic virus 1 (HTLV-1) myelitis, and others might be unique or much more common in the Middle East compared to Europe or North America, which necessitates a slightly different diagnostic approach.

2. Methodology

Neurologists from different countries in the MENA region with experience in management of MS, were selected by board members of the Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS), and met in Muscat-Oman in May 2023 at a workshop sponsored exclusively by MENACTRIMS to update the previously published consensus guidelines for diagnosis and treatment of MS (Yamout et al., 2020a). No financial contribution or sponsoring by the pharmaceutical industry was involved. The panel members represented countries in the region with specialized MS clinics/centers or dedicated neurological services to MS patients. The panel consisted of academic, hospital-based and community general neurologists with expertise in MS, along with specialized MS neurologists in order to ensure a wide diversity of opinions. The guidelines were divided into the following sections: Diagnosis of MS and red flags, radiologically isolated syndrome, clinically isolated syndrome, treatment of relapsing remitting MS, treatment of relapses, suboptimal response definition, treatment of progressive MS, pregnancy and breastfeeding, pediatric MS and autologous hematopoietic stem cell transplantation. Each section was assigned to a panel member to review and prepare final recommendations based on the most recent scientific evidence. The whole panel discussed all recommendations during the Oman meeting and after extensive deliberation agreed on all points with minimal disagreement or concerns. A recommendation was approved if at least 80 % consensus was achieved by open voting.

3. Diagnosis of Multiple Sclerosis

The diagnosis of MS remains clinical despite recent advances in diagnostics and the availability of several radiological and neuroimmunological surrogate markers. The diagnosis relies on comprehensive history taking and neurological examination to determine dissemination in time and space of certain clinical symptoms and signs while excluding mimickers in patients with clinically isolated syndrome (CIS), defined as a single episode of neurological symptoms suggestive of MS, typically involving the optic nerves, brainstem/ cerebellum, spinal cord or cerebral hemispheres. Supportive diagnostic evidence may be provided by paraclinical tests such as magnetic resonance imaging (MRI), evoked potential studies (identifying clinically silent lesions in the visual, brainstem, and spinal cord pathways) and cerebrospinal fluid (CSF) analysis (looking for inflammatory markers such as oligoclonal bands (OCB) and/or elevated IgG index). These CSF inflammatory markers are present in up to 90 % of patients with MS (Link and Huang, 2006).

The diagnostic criteria proposed by McDonald in 2001, and revised three times so far in 2005, 2010 and 2017 expanded the role of MRI in proving dissemination in space (DIS) and time (DIT), and allowed for earlier diagnosis of MS (McDonald et al., 2001; Polman et al., 2011; Thompson et al., 2018).

With respect to MRI protocol, it is recommended to adopt the 2021 MAGNIMS–CMSC–NAIMS consensus guidelines on the use of MRI in MS (Wattjes et al., 2021).

In the latest revised 2017 criteria, diagnosis of MS still requires evidence of DIS and DIT in the absence of better explanation (Thompson et al., 2018). DIS can now be fulfilled by demonstrating $\geq$ 1 T2 lesions in at least 2 out of the 4 following regions of the CNS: periventricular, cortical-juxtacortical, infra-tentorial and spinal cord. It is important to note that symptomatic lesions in the spinal cord and brain are now included in the revised criteria.

DIT can be fulfilled by the presence of a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, or the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any point in time. Again, unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required. If criteria for DIS are fulfilled, the presence of CSF-specific OCB allows a diagnosis of Multiple Sclerosis in the absence of DIT. CSF Kappa free light chains is another promising biomarker for the diagnosis of MS and might be included in future diagnostic criteria interchangeably with OCB (Arrambide et al., 2022).

The diagnosis of primary progressive MS (PPMS) relies on demonstrating retrospectively or prospectively, steady disability progression without relapses over a period of at least one year and at least two of the three following criteria:

1. One or more T2 lesions in at least one of 3 brain areas (periventricular, cortical/juxtacortical, or infratentorial region)
2. At least two or more spinal cord lesions
3. Positive oligoclonal bands by isoelectric focusing immunoassay

All revised criteria are still based on excluding other possible entities that could explain the patient's clinical and radiological findings. Patients who have atypical clinical or MRI findings should be thoroughly investigated to identify MS mimickers. A list of the most common red flags is outlined in Table 1. Although CSF analysis is not required to establish the diagnosis of MS, it is recommended to obtain CSF in atypical presentations in order to exclude other diseases, especially in pediatric patients. The potential list of MS mimickers is exhaustive, with a variety of available tests to exclude different possibilities (Table 2). Considering such diagnostic alternatives randomly has a very low yield and leads to unnecessary workup. The differential and subsequent workup should be guided by 'atypical' clinical/paraclinical findings or red flags that are specific to each case.

Radiologically isolated syndrome (RIS) refers to asymptomatic patients found on routine MRI to have lesions highly suggestive of MS. The diagnosis is based on the Okuda criteria (Okuda et al., 2009).

4. Treatment of Multiple Sclerosis

4.1. Acute relapse

Several publications demonstrated the efficacy of intravenous methylprednisolone (IV-MP) (Durelli et al., 1986; Milligan et al., 1987; Milanese et al., 1989). A Cochrane meta-analysis of oral *versus* intravenous steroids for treatment of MS relapses showed no significant difference in efficacy between the two routes of administration. There was however a trend for higher incidence of adverse events in the oral group (Burton et al., 2012). The need for oral prednisone tapering after the IVMP should be considered on an individual basis (although there are data (Perumal et al., 2008) suggesting no additional benefit for oral taper). A second course of high dose IV-MP has been recommended by certain consensus guidelines in patients failing to improve on the initial course, but no clinical evidence is available to support such approach (Rieckmann et al., 2004).

In patients with severe residual deficits who fail to respond to IV-MP,

Table 1
Red flags in the diagnosis of Multiple Sclerosis.

Clinical presentation:
• No dissemination in time/space
• Onset <10 or >55 years of age
• Prominent fever/headache, impairment of consciousness,
• Abrupt hearing loss
• Recurrent stereotyped deficits
• Non-scotomatous field defect
• Cortical features (seizures, aphasia, cortical blindness)
• Encephalopathy or insidious cognitive decline
• Headache and/or meningeal signs
• Multiple cranial neuropathies
Optic Neuritis:
• Bilateral presentation
• Severe pain that restricts movement
• Very severe or hyperacute visual loss without recovery after 1 month
• Uveitis
• Retinal exudates or hemorrhages, severe optic disc edema and vitreous reaction
• Normal brain and spinal cord magnetic resonance imaging (MRI)
• Painless visual loss
• Not responding to intravenous steroids or plasmapheresis
Transverse Myelitis:
• Hyperacute non progressive onset
• Complete involvement of the spinal segment
• Progressive myelopathy in the absence of bladder involvement
• Anterior spinal artery distribution
• Radicular pain
• Cauda Equina Syndrome
• Co-existing lower motor neuron (LMN) signs
Brainstem/Cerebellar:
• Hyperacute onset in a vascular territory
• Fluctuating or fatigable ocular or bulbar symptoms
• Complete external ophthalmoplegia
• Isolated steadily progressive course
MRI:
• Brain: Normal, small lesions < 3 mm, prominent gray matter involvement, hydrocephalus, absence of callosal or periventricular lesions, symmetric confluent WM lesions, sparing of U fibers, meningeal enhancement, simultaneous enhancement of all lesions, persistent enhancement of lesions for more than 12 weeks, thin pencil like ventricular enhancement, cloud like enhancement, marked isolated brainstem-cerebellar atrophy, complete resolution of lesions after immunosuppressive or steroid therapy, hemorrhages or micro hemorrhages
• Spine: Extensive lesion spanning 3 or more segments, cord swelling, full thickness lesions, leptomeningeal enhancement, T1 hypointense lesions, "bright spotty" T2-hyperintense lesions, bagel sign, H-sign
Cerebrospinal Fluid (CSF):
• Normal,
• Absence of oligoclonal bands (By isoelectric focusing technique)
• White blood cell count > 50
• Protein > 80 mg/dl

Table 2
Some of the unusual mimics of relapsing-remitting Multiple Sclerosis.

	Optic Neuritis/Neuropathy	Spinal Cord Syndrome/ Myelitis
Infectious	Cat scratch, syphilis, Lyme, viral neuroretinitis, toxoplasmosis, histoplasmosis	Viral: HSV, VZV, West Nile, HTLV1, EBV, CMV, HIV Syphilis, Lyme, tuberculosis, Toxocara canis, brucellosis
Inflammatory/ Autoimmune	Sarcoid, SLE, Sjögren, Behçet's, neuromyelitis optica, paraneoplastic, MOGAD, Susac disease	Sarcoid, SLE, Sjögren's, paraneoplastic, neuromyelitis optica, MOGAD
Neoplastic/ Infiltrative	Optic nerve glioma, sphenoid meningioma, metastatic tumor	Epidural metastasis, intravascular lymphoma
Vascular	Retinal artery occlusion, anterior/posterior ischemic optic neuropathy	Spinal cord infraction, cavernous angioma, Dural arteriovenous fistula
Metabolic/Toxic	Vitamin B12 deficiency, malnutrition	Nitrous oxide toxicity, vitamin B12 or copper deficiency, heavy metal poisoning
Hereditary	Leber's disease	Hereditary spastic paraplegia, spinocerebellar ataxia
Degenerative/ Structural	Retinal detachment, Cerebral aneurysm Brain Stem Syndrome	Disc herniation, epidural abscess/hematoma Cerebral/Cognitive Syndrome
Infectious	Syphilis, listeria, mycoplasma, viral/PML tuberculosis, CNS Whipple, neurobrucellosis	Cryptococcus, toxoplasmosis, cysticercosis, CNS Whipple, neurobrucellosis Viral: HSV, HHV6, VZV, EBV, CMV, enteroviruses, arboviruses
Inflammatory/ Autoimmune	Behçet, sarcoid, postinfectious cerebellitis, paraneoplastic, Bickerstaff encephalitis, myasthenia gravis, celiac disease, neuromyelitis optica, MOGAD, CLIPPERS	SLE, Hashimoto's encephalopathy, paraneoplastic, sarcoid, vasculitis
Neoplastic/ Infiltrative	Pontine glioma, Erdheim Chester disease	Cerebral ischemia, seizures, tumors, Erdheim Chester disease, Langerhans histiocytosis
Vascular	Cavernous angioma, cardioembolic stroke, dissection, aneurysms	Antiphospholipid syndrome, CADASIL
Metabolic/Toxic	Central pontine myelinolysis, alcohol	Vitamin B12 deficiency, heavy metal poisoning, serotonin syndrome, Wernicke encephalopathy
Hereditary	Spinocerebellar ataxia, basilar migraine	Mitochondrial disorders
Degenerative/ Structural	Chiari malformation, basilar invagination, abnormal vascular loops	Epidural/subdural hematoma

Abbreviations: HSV, Herpes Simplex Virus; VZV, Varicella Zoster Virus; EBV, Epstein-Barr Virus; CMV, Cytomegalovirus; HIV, Human Immunodeficiency Virus; SLE, Systemic Lupus Erythematosus; PML, Progressive Multifocal Leukoencephalopathy; CNS, Central Nervous System; HHV6, Human Herpes Virus 6; CADASIL, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MOGAD, Myelin Oligodendrocyte Glycoprotein antibody Associated Disorder; CLIPPERS, Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids.

plasmapheresis may be considered based on clinical evidence from two randomized controlled trials (RCT) (Weiner et al., 1989; Weinshenker et al., 1999). Several case series demonstrated functional neurological improvement following plasmapheresis in patients who failed to improve on IV-MP or those with severe acute exacerbations (Llufriu et al., 2009; Trebst et al., 2009; Habek et al., 2010; Magana et al., 2011). Intravenous Immunoglobulin (IVIG) is not recommended for routine use in the treatment of MS relapses given the insufficient evidence. However, in patients who have contra-indications to IV-MP and plasmapheresis, IVIG (2 g/kg over 5 days) may be used based on the available supportive data (Visser et al., 2004; Tselis et al., 2008).

4.1.1. Recommendations

It is recommended to treat acute MS relapses with a 3–5-day course of IV Methylprednisolone (IV-MP) at a daily dose of 500–1000 mg. It is appropriate to consider plasmapheresis in the treatment of patients with severe disability who fail to respond to 1, 2 courses of IV-MP.

4.2. Radiologically isolated syndrome (RIS)

The 10-year risk of developing a first demyelinating event in 277 RIS patients was estimated at 51.2 %. Age, positive CSF for OCBs, infratentorial lesions on MRI, spinal cord lesions and presence of gadolinium-enhanced lesions during follow-up were associated with the risk of a clinical event (Lebrun-Frenay et al., 2020). Several trials investigated the benefit of initiating DMTs in RIS. A multi-center, randomized, double-blinded, placebo-controlled study assessed 87 RIS patients after 1:1 randomization to Dimethyl fumarate (DMF) 240 mg bid or placebo. The risk of a first clinical demyelinating event during the 96-week study period was reduced by 82 % ($p = 0.007$) (Okuda et al., 2023). A 2-year randomized, double-blinded placebo-controlled study assessed 89 patients with RIS randomized to teriflunomide or placebo.

The risk of a first clinical demyelinating event was reduced by 62 % ($p = 0.18$) (Lebrun-Frénay, 2023).

A phase 4 multicenter, randomized, double-blind, placebo-controlled study is enrolling 100 RIS patients to assess the efficacy of ocrelizumab and identify biomarkers indicative of emerging autoimmunity as well as immune recovery after transient B-cell depletion (Longbrake et al., 2022).

4.2.1. Recommendations

Patients with RIS should be referred to a specialized MS center for further management. In the presence of multiple risk factors and evidence of new lesions on follow-up MRI, patients with RIS should be considered for treatment

4.3. Clinically isolated syndrome

The relative and absolute risk reductions for conversion to clinically definite MS over 2 years in the various RCTs were 50 % and 15–20 %, respectively (Jacobs et al., 2000; Comi et al., 2001, 2009, 2012; Kappos et al., 2006). Patients with more than 9 T2 and/or gadolinium-enhancing (Gd+) lesions benefited the most from initiating treatment (O'Connor et al., 2009). With the new revised 2017 McDonald diagnostic criteria, allowing for an earlier diagnosis of MS, the proportion of patients with CIS not fulfilling criteria for RRMS will probably be less than 10 %, taking into account the high proportion of MS patients (90–95 %) who demonstrate CSF OCB when tested by isoelectric focusing. In that respect, patients with CIS not fulfilling the 2017 MC Donald criteria, have either no evidence of dissemination in space (2 lesions in locations typical for MS) or negative CSF OCBs and no enhancing lesions. In both cases, we recommend a thorough review of the diagnosis to rule out any potential mimickers. Clinical and radiological features have been shown to be predictive of conversion to MS and future disability accumulation (Tintore et al., 2015).

4.3.1. Recommendations

Patients with CIS (*i.e.*, not fulfilling the 2017 McDonald criteria for MS) should be considered for treatment based on the following predictive factors: high MRI lesion load, severe relapse, incomplete recovery, CSF OCB and multifocal onset.

We do not advise treating patients with CIS and normal brain MRI.

4.4. Relapsing remitting Multiple Sclerosis (RRMS)

4.4.1. Disease-modifying therapies

More than twenty disease modifying therapies (DMTs) are currently approved for the treatment of RRMS, with more being added every year. All these DMTs exert their effect through different mechanisms of action including immunomodulation, interference with cell trafficking, and depletion of different immune cells.

4.4.1.1. Interferons & glatiramer acetate. Interferons-beta (IFN-beta) and glatiramer acetate (GA) are both used to treat RRMS based on class I evidence from multiple multicenter RCTs. IFN-beta can modify T and B cell activity, cytokine secretion, and T regulatory cells, while GA specifically modulates T regulatory cells. Both treatments have shown moderate efficacy in reducing the risk of relapse and disability progression by approximately 30 % (The IFNB Multiple Sclerosis study group, 1993; Jacobs et al., 1996, Ebers, 1998; Johnson et al., 1995; Rice, 2001). Early treatment with subcutaneous (SC) IFN-beta 1b has also been associated with a 47 % reduction in the hazard ratio for all-cause mortality over 21 years compared to placebo treatment (Goodin et al., 2012). PEGylated interferon-beta-1a, allows for a single dosing every two weeks and has shown similar efficacy and adverse event profile to other IFN (Calabresi et al., 2014). Double dose (40 mg) GA administered three times weekly has also demonstrated similar efficacy in recent trials (Goodin et al., 2012; Khan et al., 2017). The long-term safety data accumulated over more than two decades is a major advantage of both treatments, but their route of administration can lead to poor adherence due to acute adverse events such as injection site reactions and flu-like symptoms (Devonshire et al., 2011). Treatment should be individualized based on patient preferences, although injectable use has been declining in recent years due to the wide range of available treatment options.

4.4.1.2. Teriflunomide. Teriflunomide is a reversible inhibitor of the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH) that mediates de novo synthesis of pyrimidine in rapidly proliferating immune cells (Palmer, 2010; Claussen and Korn, 2012). Teriflunomide was the second oral DMT to receive FDA approval based on two phase III clinical trials in patients with RRMS. In the TOWER and TEMSO trials, teriflunomide at a dose of 14 mg daily reduced ARR by 36.3 % and 31 %, and the risk of disability progression by 31.5 % and 30 %, respectively when compared to placebo (Confavreux et al., 2014; O'Connor et al., 2011). When compared to IFN-beta 1a in a randomized rater-blinded study, teriflunomide did not show any difference in time to failure (defined as the first occurrence of confirmed relapse or permanent treatment discontinuation for any cause) (Vermersch et al., 2014). Overall, teriflunomide is well tolerated and safe with mild adverse events (AEs), including hair thinning, elevation of serum liver enzymes and mild leucopenia. Teriflunomide can be quickly cleared from the body within 11 days using oral cholestyramine or charcoal. In a 9-year of follow-up (O'Connor et al., 2016), the TEMSO extension study demonstrated results consistent with the core trial, with no new adverse events reported. Moreover, the TOPIC extension study has not revealed any new safety issues (Miller et al., 2019).

4.4.1.3. Dimethyl fumarate. DMF is another oral medication that has been approved for the treatment of RRMS. It is a modified fumaric acid ester that promotes anti-inflammatory and cytoprotective activities that are mediated, at least in part, by the Nrf2 antioxidant response pathway (Linker and Gold, 2013). In an integrated analysis of the 2 phase III trials DEFINE and CONFIRM, DMF 240 mg given twice daily showed a significant reduction in ARR (49 %), and disability progression (32 %) compared to placebo (Viglietta et al., 2015). DMF was generally safe and well tolerated with the most common AEs being flushing and gastrointestinal AEs. The ENDORSE study, an open label follow-up of the original trials, showed no new adverse events during 6 years of follow-up (Gold et al., 2016). As of December 31st, 2021, DMF has been administered to over 560,000 patients, with more than 1190,000 person-years of exposure. A total of 12 cases of PML were confirmed. Most cases were observed in patients with prolonged moderate to severe lymphopenia. Therefore, it is recommended discontinuing DMF treatment if grade III lymphopenia (below 0.5×10^9/L) persisted for more than six months (Jordan et al., 2022).

4.4.1.4. Fingolimod. Fingolimod is a sphingosine1-phosphate receptor (S1PR) modulator that inhibits lymphocyte egress from lymph nodes resulting in reduced infiltration of potentially auto-aggressive lymphocytes into the CNS (Mehling et al., 2011; Matloubian et al., 2004). Fingolimod was the first oral DMT approved for RRMS based on two phase III clinical trials (Kappos et al., 2010; Cohen et al., 2010). It reduced annualized relapse rate (ARR) by 55 % and 52 % compared to placebo and intramuscular (IM) IFN-beta 1a respectively, and the risk of disability progression by 30 % compared to placebo only. In a subgroup analysis of patients with highly active disease despite IFN treatment in the year preceding enrollment, fingolimod reduced ARR by 61 % relative to IFN-beta 1a IM along with reduction in lesion counts and brain volume loss (Cohen et al., 2013). In a real-world study using propensity-matched data from MSBase, patients switching to fingolimod due to breakthrough disease on first line DMTs had a 26 % reduction in

risk of first on-treatment relapse when compared to patients switching to other first line therapies such as IFN or GA (He et al., 2015). However, careful monitoring is needed due to several safety issues including bradycardia, macular edema, skin cancer and infections. First dose administration of fingolimod requires cardiac monitoring to detect any arrhythmia or conduction block. Suspicious skin lesions should be immediately reported and evaluated. As of August 31, 2022, 61 cases of progressive multifocal leukoencephalopathy (PML) have been reported on fingolimod without prior natalizumab treatment, corresponding to ≥327,600 patients treated with fingolimod and ≥1,038,100 patient-years of exposure (Novartis, 2023). Accordingly, the risk of PML on fingolimod is estimated to be 1.86/10,000 patients (95 % confidence interval [CI]: 1.42, 2.39 per 10,000 patients). Given the low risk of fingolimod associated PML, screening for John Cunningham virus (JCV) antibodies is not recommended (Roy et al., 2021).

4.4.1.5. Ponesimod. Ponesimod is a selective S1PR1 modulator with rapidly reversible pharmacological properties (Dash et al., 2018). Ponesimod has a shorter half-life and faster elimination (within 1 week) compared to fingolimod (D'Ambrosio et al., 2015). In 2021, the US Food and Drug Administration (FDA) approved ponesimod, as an oral once daily medicine, to treat adults with RRMS, CIS and active secondary progressive MS (SPMS). In the phase III OPTIMUM trial (Kappos et al., 2021), ponesimod (20 mg/day) reduced the ARR by 30.5 % and combined unique active lesions per year on MRI by 56 % compared to teriflunomide. However, the reduction in confirmed disability accumulation was not statistically significant compared to teriflunomide. The adverse events profile of ponesimod was similar to other S1PR modulators but with lower rates of bradycardia and long-term lymphopenia compared to fingolimod (Ruggieri et al., 2022).

4.4.1.6. Siponimod. Siponimod is a selective sphingosine1-phosphate receptor ($S1P_{1,5}$) modulator that inhibits lymphocyte egress from lymph nodes resulting in reduced infiltration of potentially autoaggressive lymphocytes into the CNS (Selmaj et al., 2013) . Its mechanism of action is similar to fingolimod but with more S1P receptor selectivity, higher blood brain barrier penetrance and a shorter half-life leading to a faster lymphocyte counts recovery to baseline levels (within 10 days following drug discontinuation) (Gentile et al., 2016). It was approved by the FDA for CIS, RRMS and active SPMS. In the phase II trial BOLD, siponimod at the approved dose of 2 mg/day reduced new and Gd+ lesions by 72 % and ARR by 66 % compared to placebo over a period of 6 months (Selmaj et al., 2013). This effect was sustained during a 24 months dose-blinded extension of the study (Kappos et al., 2016). With a dose titration over 10 days in the extension study, no case of symptomatic bradycardia was reported, probably due to its S1P receptor selectivity. In the EXPAND trial, siponimod at a dose of 2 mg/day reduced relapse rate by 55 % in patients with SPMS (Kappos et al., 2018a).

The adverse event profile of siponimod was similar to other drugs of the same class including elevation in liver enzymes, macular edema, hypertension, seizures and Varicella-Zoster reactivation (Kappos et al., 2018a).

Siponimod is contraindicated in patients homozygous for CYP2C9*3 (CYP2C9*3/*3 genotype) due to the potential long-term safety implications in CYP2C9 poor metabolizer treated with this drug. In patients with a CYP2C9 *1/*3 or *2/*3 genotype, after treatment titration, the recommended maintenance dosage is 1 mg taken orally once daily starting on Day 5 (Roy et al., 2021).

4.4.1.7. Cladribine. Cladribine is a nucleoside analogue of deoxyadenosine that accumulates within cells, resulting in inhibition of DNA synthesis and repair, and subsequent apoptosis, with preferential affection of lymphocytes (Leist and Weissert, 2011). It was approved in Europe in 2017 as an initial treatment of RRMS patients with high disease activity or patients failing other DMTs and in the USA in 2019 for patients with RRMS failing other DMTs or with active SPMS. In a randomized controlled phase III trial, cladribine at a dose of 3.5 mg/kg, administered as oral tablets in four cycles of 5-day duration each on months 1, 2, 13 and 14 of the 2 year-long trial, reduced ARR by 58 % and risk of 6-months confirmed disability progression by 47 % compared to placebo (Giovannoni et al., 2010). In the extension trial, patients shifted to placebo for the next 2 years showed persistent efficacy of the treatment with 77.8 % and 75.6 % of patients remaining relapse free during the first 2 years and years 3 and 4 of the extension respectively, presumably due to immune reconstitution (Giovannoni et al., 2010). Accordingly, cladribine was approved as two treatment courses during the first 2 years with no further therapy required in years 3 and 4. Cladribine showed a good safety profile with similar infection and severe infection rates compared to placebo except for slight increase in herpes zoster infections (Giovannoni et al., 2010). Cladribine induces transient lymphopenia that starts recovering by 6-months post-dose. With the currently approved regimen and dosing guidelines, only 5 % of patients developed Grade III lymphopenia during the extension phase and none had Grade IV lymphopenia (Giovannoni et al., 2010).

4.4.1.8. Natalizumab. Natalizumab was the first approved monoclonal antibody for RRMS (Pucci, 2011). It is a selective adhesion molecule inhibitor that interferes with the influx of inflammatory cells into the brain by binding to the α_4 subunit of $\alpha_4\beta_1$ integrin expressed on the surface of immune cells, preventing its interaction with the vascular cell adhesion molecule (VCAM1) on the endothelial cells (Baron et al., 1993). In the phase III AFFIRM trial, natalizumab reduced the rate of clinical relapses by 68 % and the risk of sustained disability progression by 42 % compared to placebo (Polman et al., 2006). This was supported by extensive post-marketing data, reporting improved efficacy in patients switched from first line therapies due to suboptimal response (Prosperini et al., 2012; Fernandez et al., 2012; Lanzillo et al., 2012, 2013; Kalincik et al., 2015; Kappos, 2018). However, due to the risk of PML which is estimated at around 4.22 per 1000), it was often used in patients failing first line therapy or those with aggressive disease. Seropositivity for JCV antibodies, prior use of immunosuppressants and duration of natalizumab treatment of more than 2 years increase the risk of PML (Sorensen et al., 2012). The prevalence of JCV antibodies in MS patients is approximately 50–60 % with an 8.5–11.7 % annual rate of seroconversion (Schwab et al., 2016; Alroughani et al., 2016). The risk of PML can be stratified further by quantifying serum antibody levels, measured as antibody index (AI), but only in patients without previous immunosuppression (Koendgen et al., 2016). The risk of PML remains significantly low in seronegative patients (0.1/1000), in seropositive patients with less than 2-years of treatment and no prior use of immunosuppressants (0.7/1000) and in seropositive patients with AI $\leq$ 0.9 and no prior use of immunosuppressants, up to 6 years of treatment (0.6/1000). The risk however increases significantly reaching 10/1000 in seropositive patients with AI $>$ 1.5 or prior exposure to immunosuppressants, and treated with natalizumab for more than 2 years (Biogen, 2014; Plavina et al., 2014). On the other hand, natalizumab remains one of the well-tolerated DMTs with low incidence of hypersensitivity reactions (Polman et al., 2006). Recent data shows that increased dosing interval of natalizumab up to 6–8 weeks does not affect efficacy and might decrease the risk of PML (Yamout et al., 2018a; Zhovtis Ryerson et al., 2016, Zhovtis Ryerson, 2019). In a recent phase III clinical trial (NOVA) (Foley et al., 2022), patients were randomized to natalizumab once every 4 weeks or once every 6 weeks after being stable for at least 12 months without relapses on once every 4 weeks dosing. The efficacy was similar between the two groups as assessed by the number of new or enlarging T2 lesions at week 72 (Foley et al., 2022).

If natalizumab is initiated in patients who are seronegative for JCV, it is recommended to test for the antibody every 6-months. In patients on no previous immunosuppressants and who are seropositive for JCV, or

seroconvert during therapy, with an antibody index ≥ 0.9, or in seropositive patients with prior immunosuppressant use, it is recommended to reassess benefit/risk ratio after 2 years of treatment with natalizumab. Extended interval dosing might also be considered for such patients, although long term safety data is not available.

A SC formulation of natalizumab was approved by the European Medicines Agency (EMA) in 2021. A Phase I pharmacokinetic study (DELIVER) (Plavina et al., 2016) in natalizumab-naive patients demonstrated that the pharmacokinetic and pharmacodynamic parameters after repeated SC dosing of natalizumab every 4 weeks were comparable to those of the intravenous (IV) route. A Phase II trial (REFINE) studying the efficacy of IV *vs* SC natalizumab every 4 weeks showed comparable efficacy between the two routes (Trojano et al., 2021). The evidence for sustained efficacy of subcutaneous natalizumab beyond 4 weeks is still inconclusive. Although the label requires monitoring during each injection in the clinic or hospital, it is acceptable to allow self-administration at home if no adverse events occur with the first 3 injections.

4.4.1.9. Alemtuzumab. Alemtuzumab is a humanized monoclonal antibody that has been approved for the treatment of RRMS. Alemtuzumab targets the CD52 surface protein that is present at high levels on T and B lymphocytes and, to a lesser extent, on other immune cells. In two phase III RCTs (CARE-MS I and II) (Cohen et al., 2012; Coles et al., 2012) that included either treatment-naive patients or patients with relapses on IFNB/GA, alemtuzumab at a dose of 12 mg/day was associated with 55 % and 49 % reduction in the risk of relapse respectively compared to IFN-beta (IFNB)1a SC. In patients with previous relapses on IFNB/GA, the risk of disability progression was reduced by 42 % compared to IFNB. In a 9-year follow-up of both trials, 62 % of patients were free of 6-month confirmed disability worsening, and 50 % had 6-month confirmed disability improvement (Ziemssen et al., 2020) . Besides infusion-related reactions and initial increase in infection rate, the major drawback was related to delayed secondary autoimmune events with peak incidence in the third year of therapy, including thyroid disease (40 %), immune thrombocytopenia (1, 2 %), and rare cases of anti-glomerular basement membrane disease (Fox and D Brassat, 2016). More AEs have been recently reported with alemtuzumab including stroke, listeria meningitis, acute coronary syndrome, acute pneumonitis and other autoimmune disorders (Buonomo et al., 2018; Ferraro et al., 2018) leading to restriction of its use to third line therapy.

4.4.1.10. Ocrelizumab. Ocrelizumab is a recombinant humanized monoclonal antibody that binds to CD20 protein on the surface of B lymphocytes, leading to the selective depletion of CD20-positive B lymphocytes by different mechanisms (Hauser et al., 2017). Ocrelizumab is administered intravenously at two doses of 300 mg two weeks apart at the onset of therapy and 600 mg every six months. It was approved by the FDA and EMA for both RRMS and PPMS in 2017. In two similarly designed phase III trials (Opera I and II) involving patients with RRMS, ocrelizumab reduced ARR by 46–47 % and risk of 24 weeks confirmed disability progression by 37–43 % compared to IFNB-1a 44 ug 3x/week (Hauser et al., 2017). Ocrelizumab showed a good safety profile with lower incidence of serious infections compared to IFNB and a similar overall incidence of serious adverse events. A slight increase in the incidence of breast cancer was seen in the ocrelizumab arm compared to IFNB, but was within the normal range for age-matched controls in different international MS registries. In a seven-year safety outcome of MS patients who took ocrelizumab across eleven clinical trials, 3 % (181 out 5680) discontinued ocrelizumab due to adverse events; four died due to infections, and four other deaths were attributed to malignancies. The cancer risk was not increased compared to population-wide age and sex-matched cohorts (Hauser et al., 2021). Similar to rituximab, ocrelizumab use was associated with increased risk of COVID-19 infection and reduced humoral response to vaccination (Apostolidis et al., 2021; Simpson-Yap, 2022). Refer to the rituximab section for further discussion regarding COVID-19 and anti-CD20 treatment.

The results of the Phase III, non-inferiority, randomized, study comparing SC and IV Ocrelizumab in 236 patients with RRMS and PMS (Ocarina II) were released in July 2023. Ocrelizumab SC was shown to be non-inferior to IV ocrelizumab, as measured by pharmacokinetics and MRI lesion activity in the brain over 12 weeks. The safety profile of both preparations was also similar (Genentech, 2023).

4.4.1.11. Ofatumumab. Ofatumumab is a human IgG1 kappa monoclonal antibody approved for the treatment of MS and exerts its effects through depleting B lymphocytes by binding to the CD20 protein (Zhang, 2009). In 2021, the FDA approved a SC formulation to treat CIS, RRMS, and active SPMS. Unlike other anti-CD20 medications, ofatumumab is a fully human monoclonal antibody given as monthly SC injections of 20 mg. Ofatumumab was superior to teriflunomide in two phase-3 randomized controlled clinical trials ASCLEPIOS I and II where 900 patients were enrolled in each arm (Hauser et al., 2020). In both trials, ARR was significantly reduced in patients receiving ofatumumab (0.11 & 0.10) when compared to patients receiving teriflunomide (0.22 & 0.25). Moreover, subjects on ofatumumab had a significantly reduced risk of confirmed disability worsening at 3 and 6 months with a hazard ratio of 0.7 (Hauser et al., 2020). There was also a significant difference in the number of gadolinium-enhancing lesions and new T2 lesions favoring ofatumumab. The two trials did not show a difference in disability improvement between the two medications.

Regarding adverse events, injection site, and injection-related systemic reactions were the most common in Phase III clinical trials (11 % and 20 %, respectively) (Hauser et al., 2020). Five patients receiving ofatumumab were diagnosed with cancer in the two trials compared to four in the teriflunomide group. No deaths were reported in the ofatumumab group, although 2.5 % of patients had serious infections.

Like other medications that chronically deplete B lymphocytes, patients receiving ofatumumab might have reduced humeral response to immunizations, a consideration for patients at increased infection risk (Faissner, 2022). Recently, a study reported the safety outcome of 1969 patients who used SC ofatumumab every four weeks in clinical trials (Hauser et al., 2022). The median time at risk, defined as the time from the first dose of ofatumumab until 100 days after the last dose, was 21 months (range was 0.0–51.8). About 5.8 % of patients discontinued the medication due to adverse events. Infections were reported in 54 % of patients, primarily nasopharyngitis, upper respiratory tract infections, and COVID-19 infections. Furthermore, about 3 % of patients had serious infections. Malignancies occurred in 11 patients (0.6 %) during the observation period. As expected, serum immunoglobulins were reduced. About 23 % and 1.5 % of patients had IgM and IgG levels below the lower limit of normal, respectively

4.4.1.12. Ublituximab. Ublituximab is a chimeric anti-CD20 monoclonal antibody that is glycoengineered by removing a sugar residue "fucose" to facilitate the engagement with effector cells through FcγRIIIa/CD16 as this will potentially lead to more efficient depletion of B lymphocytes through antibody-dependent cellular cytotoxicity (ADCC) (de Romeuf et al., 2008). Two identical, phase 3, double-blind, double-dummy trials (ULTIMATE I and II) examined the efficacy of ublituximab compared to teriflunomide in patients with Multiple Sclerosis (Steinman et al., 2022). Ublituximab was administered as an IV infusion (150 mg on day one, followed by 450 mg on day 15 and weeks 24, 48, and 72), all given over 1 h. Over a thousand patients were enrolled across the two trials and followed up for a median of 95 weeks. Compared to teriflunomide, ublituximab was associated with significantly lower number of relapses (rate ratio of 0.41 in ULTIMATE I and 0.51 in ULTIMATE II) (Steinman et al., 2022). The efficacy of ublituximab was even more pronounced on MRI measures. In ULTIMATE I, the

mean number of gadolinium-enhancing lesions was 0.02 compared to 0.49 in subjects on teriflunomide (rate ratio of 0.03). Infusion-related reactions were the most common adverse event occurring in nearly half of the patients. Of note, infusion over 1 h did not lead to a significant increase in infusion reactions (Steinman et al., 2022). Subsequently, ublituximab was approved by the FDA for adult patients with CIS, RRMS, and active SPMS.

4.4.1.13. Rituximab. Rituximab (RTX) is a chimeric monoclonal antibody that depletes B lymphocytes, currently approved in B-cell malignancies, rheumatoid arthritis, Wegener granulomatosis, and microscopic polyarthritis. The drug is widely used off-label in other systemic and neurological immune-mediated disorders such as neuromyelitis optica and myasthenia gravis (Kosmidis and Dalakas, 2010). Off-label use of RTX in MS has increased considerably (Berntsson et al., 2018) following a phase 2 trial that demonstrated its positive effects in patients with RRMS (Hauser et al., 2008). Several open-label or observational studies from Sweden and other parts of the world supported the efficacy and safety of RTX in comparison to other DMTs in patients with MS (Rahmanzadeh et al., 2018; Spelman et al., 2018; Naismith et al., 2010; Salzer et al., 2016). A multicenter randomized phase 3 clinical trial (RIFUND-MS) compared RTX to dimethyl fumarate in patients with RRMS and CIS, with about one hundred patients in each group (Svenningsson et al., 2022). Three (3 %) patients in the RTX group and 16 (16 %) patients in the dimethyl fumarate group had a relapse during the trial, corresponding to a risk ratio of 0·19 (95 % CI 0·06–0·62; p = 0·0060). In another study (Alping et al., 2016), Alping et al. (2016) compared the efficacy of fingolimod and RTX in patients with relapsing MS following cessation of natalizumab due to JCV positivity. After 1.5 years, there was a significant difference between the patients receiving RTX and fingolimod in relapse rate (1.8% *vs.* 17.6 %) and new Gd+ lesions on MRI (1.4 % *vs.* 24.2 %). Rituximab has been commonly used in the Middle East. In an observational study (Yamout et al., 2018b), Yamout et al. (2018b) reported their experience with RTX in 89 patients (59 with RRMS and 30 with PMS). They demonstrated a reduction of ARR from 1.07 at baseline to 0.11 in RRMS ($p < 0.0001$) and from 0.25 to 0.16 in PMS patients ($p = 0.593$). They also reported no evidence of clinical or radiological activity (new T2 or enhancing lesion) in 74 % of their patients after one year of treatment with RTX (). Although no phase III controlled studies are available, RTX share of the DMTs market is rapidly increasing in some countries like Sweden (Berntsson et al., 2018). A significant advantage of RTX is wider availability, long-term safety data, and lower cost compared to recently approved anti-CD20 medications. This, in addition to its convenient infrequent dosing, makes RTX of considerable use in countries where newer DMTs, usually more expensive, are not readily available or affordable or in special populations such as refugees or in places where political or economic instability or wars, makes access to healthcare inconsistent and unpredictable (Zeineddine and Yamout, 2020; Mathew et al., 2020; Rezaee et al., 2022). Based on the literature, the dosing of RTX is not fixed but an induction dose of 1000 mg followed by a maintenance dose of 500–1000 mg every 6 months is most commonly used. RTX is relatively well tolerated with low incidence of infusion reactions and elevation of liver function tests.

As a medication that completely depletes B lymphocytes in most patients, the risk of hypogammaglobulinemia and infections increases. A large population-wide observational study showed that patients with Multiple Sclerosis treated with RTX were at increased risk of serious infections and hospitalization compared to natalizumab or fingolimod (Luna et al., 2020). During the COVID-19 pandemic, most MS patients on RTX did well when they contracted the infection. However, compared to non-CD20 targeting DMTs, RTX and ocrelizumab were associated with an increased risk of severe infection and risk of hospitalization (Simpson-Yap et al., 2021; Sormani et al., 2021). Expectedly, the humoral response to COVID-19 vaccines was reduced in patients receiving rituximab and ocrelizumab, although the cellular response is less affected (Apostolidis et al., 2021).

Few biosimilars to RTX have been developed and are increasingly used for different indications, including MS (Naser Moghadasi et al., 2019; Perez et al., 2021). The published data generally show a similar profile to RTX, although the studies were not prospective, randomized, or blinded. Biosimilars will offer a more affordable alternative to RTX, although further studies are needed. If a biosimilar is used, careful follow-up and monitoring of efficacy and adverse events are warranted.

4.4.2. Treatment algorithm for RRMS patients

Given the increasing number of available DMTs, different treatment strategies have been proposed for treatment initiation in patients with RRMS due to lack of class 1 evidence comparative data between the newer agents. Comparing across trials with different designs and baseline characteristics is associated with inherent limitations (Cohen et al., 2010, 2012; Coles et al., 2012; Hauser et al., 2017). Therefore, evidence-based medicine from controlled trials must be supplemented by real world evidence derived from large international and national registries and if need be, expert opinion, in order to decide on the best therapeutic option available for an individual patient. Ideally, the treatment should be individualized based on different biological and radiological biomarkers. Taking all the of the above into consideration, we developed an algorithm for the treatment of MS based on the available scientific evidence, approved FDA and EMA indication labels, and expert opinion.

4.4.2.1. Treatment naïve-patients. Pathological studies have shown that axonal loss is highest in acutely inflamed lesions (Trapp et al., 1998), yet disability is hardly detected in the early stages of the disease due to intrinsic compensatory mechanisms through neuroplasticity (Zatorre et al., 2012). However, with continuous inflammatory activity the "brain reserve" will ultimately be exhausted, leading to accumulation of disability. In addition, growing evidence is suggesting that in the early stages of the disease, most of the disability is not due to relapses but rather to progression independent of relapse activity (PIRA) (Kappos et al., 2018b, 2020). It is therefore imperative to start DMTs early once the diagnosis of RRMS is established in order to reduce inflammation and secondary axonal loss in the CNS (Hillert, 2021). On the other hand, recent studies have consistently shown that starting high efficacy compared to moderate efficacy DMTs early on to limit inflammation, axonal loss and ultimately disability, improves long term outcomes. In a retrospective study from the MSBase registry, initial treatment with high efficacy DMTs compared to moderate efficacy DMTs was associated with a significantly decreased risk of transitioning to secondary progressive MS (hazard ratio [HR] 0.66, 95 % CI 0.44; 0.99, $p = 0.046$) with a 5-year absolute risk of 7 % *vs* 12 %) (Brown et al., 2019). In a retrospective study from the MSBase registry and the Swedish MS registry, early use of high efficacy DMTs (0–2 years from disease onset) was associated with a significantly lower EDSS score after 6 years as compared to later use (4–6 years from disease onset) (He et al., 2020). In a retrospective comparison of the Swedish and Danish national MS registries, 34.5 % and 7.6 % of patients, respectively were initiated on high efficacy DMTs. Patients in the Swedish registry had a 29 % reduction in the risk of confirmed disability worsening (HR 0.71 [95 % CI 0.57; 0.90], p = 0.004) (Spelman et al., 2021).

A growing number of studies have shown that high disease activity (HDA) early in the course of the disease is predictive of future disability accumulation (Confavreux et al., 2003; Tintore et al., 2015). Unfortunately, there is no current consensus on defining highly active disease in RRMS. The following clinical and radiological prognostic factors should be taken into consideration when determining if a patient has highly active disease:

- Relapse frequency in the previous year ($\geq$ 2 relapses)

- Relapse severity (pyramidal/cerebellar systems involvement)
- Incomplete recovery from relapses
- High T2 lesion load on MRI
- Spinal lesions
- Infratentorial lesions
- Multiple Gadolinium enhancing lesions.

A subgroup of patients with high disease activity will follow a rapidly evolving aggressive course. Although no clear definition of rapidly evolving aggressive disease (READ) is agreed upon, common to all definitions is the early accumulation of disability along with high relapse frequency and disease activity on MRI. Menon et al. defined aggressive MS as patients reaching an EDSS score of 6.0 within 5 years of disease onset or by 40 years of age (Menon et al., 2013). In their review of the British Colombia MS database, 14.3 % of patients fulfilled either one of the two definitions, 86 % of whom were relapsing remitting. Rush et al. (2015) defined aggressive MS in treatment naïve patients as 2 or more relapses with incomplete recovery in the past year. The EMA definition of rapidly evolving severe disease was $\geq$ 2 disabling relapses in 1 year with $\geq$1 Gd+ lesion or significant increase in T2 lesion load. Accordingly, we defined READ as the presence of 2 or more disabling relapses with incomplete recovery in the previous year and a high T2 lesion load on MRI.

4.4.3. Recommendations

In treatment naïve patients with moderately active disease, moderate efficacy DMTs such as IFN-beta, GA, teriflunomide, or DMF can be initiated, in addition to high efficacy DMTs with acceptable safety profiles such as S1PR modulators, cladribine, B-cell depleting therapies with adequate long term follow-up and natalizumab in JCV seronegative patients.

In patients with highly active disease, S1PR modulators, cladribine, B-cell depleting therapies or natalizumab should be initiated following careful risk stratification and evaluation of comorbidities.

In patients with rapidly evolving aggressive disease, natalizumab, B cell depleting therapies or alemtuzumab are recommended after careful risk stratification and evaluation of comorbidities.

Rituximab can be used off label for all levels of activity in special populations such as refugees, or in countries where other appropriate options are either not available or unaffordable

4.4.3.1. Suboptimal responders with breakthrough disease. This term has been interchangeably used with treatment failure, or treatment non-responders. To date, there is no consensus definition of response failure, however, there is general agreement that disease activity while on a DMT with full adherence for 6–12 months, in the form of clinical relapse, MRI new/enlarging/enhancing lesions or disability progression, indicate a suboptimal response (Río et al., 2009; Rotstein et al., 2015; Sormani et al., 2016; Montalban et al., 2018; Rae-Grant et al., 2018; Freedman et al., 2020). The advent of more potent therapies has made the "No Evidence of Disease Activity' outcome measure, as defined by absence of relapses, new MRI lesions and disability progression, more attainable. However, no single therapeutic strategy to date, including autologous hematopoietic stem cell transplantation (AHSCT), could achieve a 100 % NEDA-3 with up to 7 years follow-up (Gasperini et al., 2019).

Although we still lack a clear definition of breakthrough disease, most current criteria are based on clinical relapses, MRI activity, and accumulation of disability. Any relapse during the first year of treatment is predictive of disability progression and treatment failure (Sormani et al., 2016; Daruwalla et al., 2023), although relapses involving pyramidal, cerebellar, brainstem, or bowel/bladder function have been associated with worse disability accrual (Stewart et al., 2017). It is of note, that most definitions of suboptimal response were derived from studies investigating the degree of response to interferon-beta.

The multicenter MAGNIMS study showed that the presence of 3 new T2 lesions on MRI 1 year after treatment initiation was predictive of treatment failure (Sormani et al., 2016, 2018; Prosperini et al., 2020). The modified Rio score was also predictive of disability progression in the presence of 3 new T2 lesions on MRI 1 year after starting treatment (Río et al., 2017). However, in both studies no rebasing of MRI at 6 months after treatment initiation was performed, and therefore some of the new T2 lesions may have occurred before onset of the DMT effect. Interestingly, the Rio study showed that either 3 new T2 lesions or 2 Gd+ lesions (indicative of new lesions after onset of DMT effect) are predictive of disability progression. Prosperini et al. (2020) reached the same conclusion, showing that the presence of Gd+ lesions is associated with future disability without the need of 3 new T2 lesions.

The two currently available DMTs labeled as immune reconstitution therapy (IRT) are alemtuzumab and cladribine. Both are given as two intermittent cycles during the first and second year of treatment. They are considered to generate changes in immune regulatory networks that can be durable in some individuals and are associated with disease remission in the absence of continuous therapy (Ceronie et al., 2018). Suboptimal response to either drug will probably not be reliably assessed until at least 6 months following completion of the full treatment protocol *i.e.* 18 months after treatment initiation. Disease activity was seen in around 15 % of patients on alemtuzumab in the CARE-MS I trial during the first year of treatment but did not affect long term remission rates from year 3 on (Wiendl et al., 2018). In a pooled CARE-MS I and CARE-MS II analysis, patients with breakthrough disease requiring a third course of alemtuzumab beyond 2 years of therapy maintained a prolonged remission (TRaboulsee et al., 2018). Accordingly, in patients with suboptimal response on alemtuzumab beyond the initial 2 years of treatment, a third course is recommended before shifting to a different therapy. Management of patients with suboptimal response on cladribine was recently addressed in a review of the literature and expert opinion recommendations by 14 international MS experts (Oreja-Guevara et al., 2023). The proportion of patients relapsing within the first 12 months was low, ranging from 1.1 to 21.9 %, and occurring particularly in patients switching from anti-lymphocyte trafficking agents (*e.g.*, fingolimod, natalizumab). Reported rates of disease activity after the full therapeutic effect of cladribine has been achieved (end of Year 2, 3 or 4) ranged from 12 to 18.7 %. Four studies reported on longer-term efficacy beyond Year 4 of treatment (Patti et al., 2020; Leist et al., 2020; Giovannoni et al., 2021; Yamout et al., 2020b). They all reported long-term follow up of patients who took part in the initial clinical trials for cladribine: disease activity was reported in 30–50 % of patients. The final recommendations were to administer the full indicated cumulative dose of cladribine in case of disease reactivation during the first year except for the rare cases of paradoxical worsening of the disease (Wehrum et al., 2018). In case of disease reactivation in years 2–4, the two recommended options were either administration of a third cladribine course or switching to another DMT. Patients with disease reactivation in year 5 and beyond were considered "cladribine responders" and should be administered a third and possibly fourth course of treatment. In patients with no disease activity in year 5 and beyond, and in view of the long-term disease control in 30–50 % of patients, the consensus was no further treatment, with regular close monitoring (MRI every 6–12 months, assessment of patient-reported outcomes [PROs], fatigue, bladder function and cognition, and biomarkers such as neurofilament light chain [NfL]).

4.4.4. Recommendations

In patients with moderately active disease and suboptimal response to first-line therapies as defined above, treatment escalation to S1PR modulators, natalizumab, B cell depleting therapies or cladribine should be considered. In patients with HDA and suboptimal response to DMTs, treatment escalation to natalizumab, B cell depleting therapies cladribine or alemtuzumab should be considered. In patients with READ and suboptimal response to the initial DMT, a lateral shift among

alemtuzumab, B cell depleting therapies and natalizumab or AHSCT should be considered. The choice among them should be based on risk stratification including serum anti-JCV antibody, prior immunosuppressant use and comorbidities (Fig. 1).

In patients on alemtuzumab fulfilling criteria for suboptimal response beyond the first 2 years of treatment, a third course of DMT is recommended before shifting to another therapy. In patients on cladribine, with suboptimal response in the third and fourth year of treatment, a third course of cladribine may be administered or shifting to one of the monoclonal antibodies. Beyond the fourth year, and in case of suboptimal response it is recommended to administer a third and possibly fourth course keeping in mind that data supporting such approach with cladribine is still limited.

Rituximab can be used off label for all levels of activity in special populations such as refugees, or in countries where other appropriate options are either unavailable or unaffordable.

In patients with evidence of breakthrough disease on any of the second line medications, a lateral switch based on the risk stratification strategy mentioned above or AHSCT should be considered before resorting to third line therapies including cyclophosphamide or mitoxantrone.

4.5. *Treatment of progressive MS*

The treatment options for progressive MS are generally limited, but positive results are starting to emerge from newly tested drugs (Sorensen et al., 2020). Early studies focused on IFN-beta and mitoxantrone (La Mantia et al., 2013).

Mitoxantrone is a cytotoxic agent that acts by intercalating with DNA and inhibiting the topoisomerase II enzyme activity for DNA repair (Durr et al., 1983). It was approved by the FDA for treatment of progressive MS based on a small phase III trial including 194 patients, considered to represent at best class II/III evidence due to inadequate blinding and small numbers (Hartung et al., 2002). A Cochrane review evaluating 3 trials, with 221 patients, showed that mitoxantrone reduced disability progression and relapse rate in the short term (two years). Its use in clinical practice however, has decreased significantly in recent years due to high rate of serious adverse event including cardiotoxicity (12 %) and leukemia (0.8 %) (Martinelli Boneschi et al., 2013).

Ocrelizumab is the only FDA approved drug that has been shown to be effective in PPMS based on the ORATORIO trial that showed a 25 % reduction in the risk of 24 week confirmed disability progression compared to placebo (Montalban et al., 2017). The patients recruited were ≤55-year-old, with a disease duration ≤10–15 years and an EDSS 3.0–6.5 at screening. Such positive results cannot be extrapolated to patients not fulfilling these inclusion criteria. Although ORATORIO trial was not powered to show differences between subgroups, a more pronounced treatment benefit was seen in patients with baseline Gd+ lesions and age ≤ 45 years. Therefore, ocrelizumab should be considered for patients with PPMS who are not wheelchair bound with radiological evidence of disease activity. An ongoing phase III trial will further evaluate safety and efficacy of ocrelizumab in older, more disabled PPMS patients (O'HAND trial) (The US National Library of Medicine, 2023a).

Interestingly rituximab, a chimeric anti-CD 20 monoclonal antibody failed in the OLYMPUS trial to show any superiority to placebo in patients with PPMS (Hawker et al., 2009). The main difference between the two trials was younger age and shorter disease duration in ORATORIO (mean age 44.7 vs 50.1years; mean disease duration 2.9 vs 4.1 years). In a subgroup analysis of the OLYMPUS trial, rituximab significantly reduced disability progression *versus* placebo in patient aged < 51

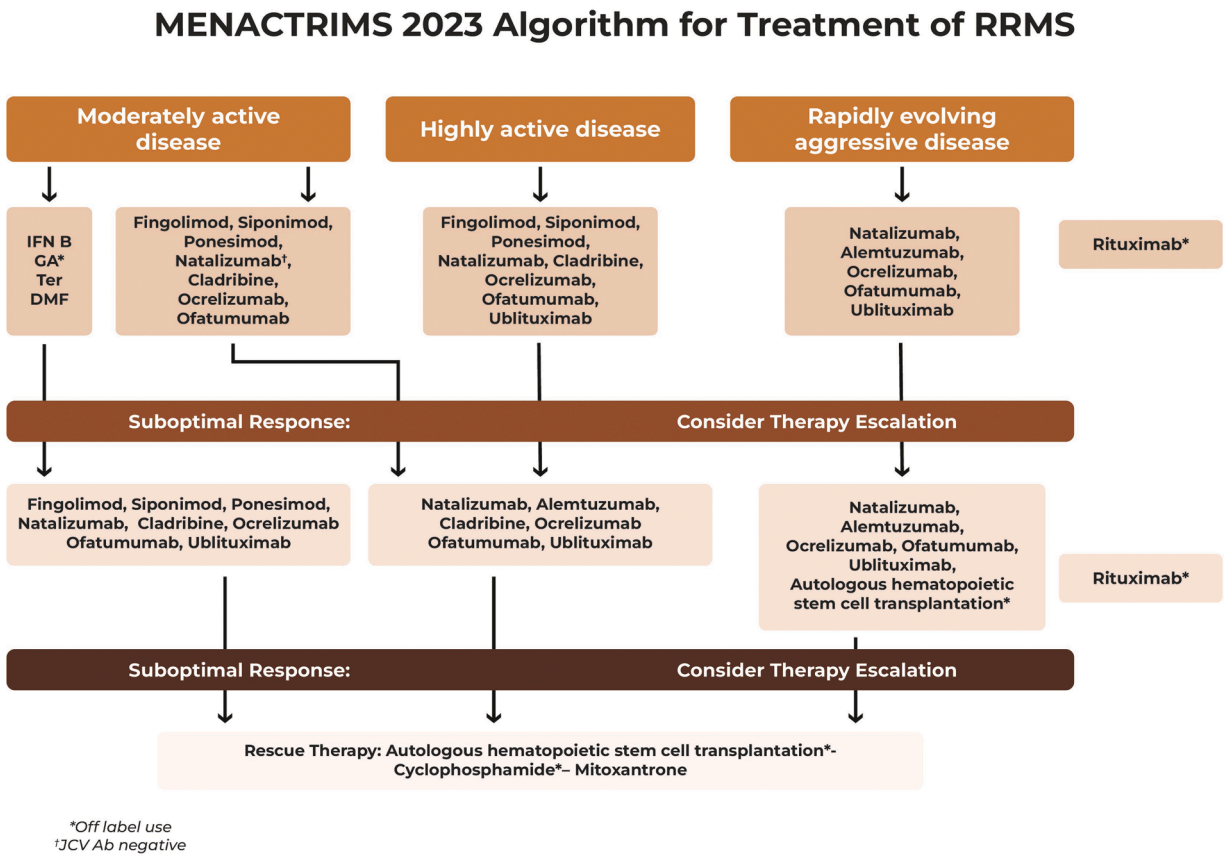

Fig. 1. 2023 Algorithm for the management of relapsing-remitting Multiple Sclerosis
Abbreviations: RRMS: Relapsing-remitting Multiple Sclerosis; IFN B: Interferon beta; GA: Glatiramer Acetate: Ter: Teriflunomide; DMF: Dimethyl Fumarate.

years with one or more Gd+ lesion at baseline (Hawker et al., 2009). These results indicate that the greatest benefit from B-cell depleting therapies is seen in PPMS patients who are younger and have active disease (Signori et al., 2018).

Siponimod is a second generation S1P receptor modulator, with selectivity to S1P1 and S1P5 receptors. In a phase III trial involving 1651 patients with SPMS siponimod at a dose of 2 mg/day was associated with 26 % reduction in 6 months confirmed disability progression and 23.4 % less brain atrophy compared to placebo, both of which were statistically significant (Kappos et al., 2018a). Patients recruited were ≤ 60-year-old with an EDSS ≤ 6.5. However, in patients without relapses in the previous 2 years or Gd+ lesions on baseline MRI, the effect on disability progression was not statistically significant. Siponimod was approved by the FDA for treatment of active SPMS.

In a recent study of patients with active SPMS by the Italian Bone Marrow Transplantation Study Group (Boffa et al., 2023), 79 AHSCT-treated patients and 1975 patients treated with other DMTs (IFN beta, azathioprine, glatiramer-acetate, mitoxantrone, fingolimod, natalizumab, methotrexate, teriflunomide, cyclophosphamide, dimethyl fumarate, and alemtuzumab) were matched using propensity scoring. Time to first confirmed disability progression was significantly longer in transplanted patients (hazard ratio [HR] = 0.50; 95 % CI = 0.31–0.81; p = 0.005), with 61.7 % of transplanted patients free from confirmed disability progression at 5 years. Patients who underwent AHSCT were more likely to experience a sustained disability improvement: 34.7 % of patients maintained an improvement 3 years after transplant *vs* 4.6 % of patients treated by other DMTs ($p < 0.001$) (Boffa et al., 2023).

Other immunosuppressants such as cyclophosphamide, methotrexate and mycophenolate were evaluated in either single arm or small open-label unblinded trials, with suggested effects on short term disability progression. Such results however were not confirmed by large scale randomized placebo-controlled trials (Goodkin et al., 1995; Zéphir et al., 2004; Frohman et al., 2005).

4.5.1. Recommendations

Consider treatment with siponimod or B-cell depleting therapies in patients with active SPMS, age ≤ 60 years and EDSS ≤ 6.5 (*i.e.* not wheelchair bound). In patients without evidence of disease activity, treatment might be considered in younger ambulatory patients in whom progression started recently.

Consider treatment with ocrelizumab for patients with PPMS, age ≤ 55 years, EDSS ≤ 6.5 (*i.e.* not wheelchair bound) and disease duration ≤ 10–15 years.

Where Ocrelizumab is inaccessible, other B-cell depleting therapies can be used.

In patients with active progressive MS not responding to siponimod or ocrelizumab, consider treatment with autologous hematopoietic stem cell transplantation.

In ambulatory patients with active SPMS not responding to siponimod or ocrelizumab or who have no access to these medications, a trial of cyclophosphamide, methotrexate, or mycophenolate may be warranted.

4.6. Autologous hematopoietic stem cell therapy

Autologous hematopoietic stem cell transplantation (AHSCT) is considered as one of the therapeutic options for MS patients with breakthrough disease on high-efficacy (Nabizadeh et al., 2022). Stem cell therapy mechanism of action is most likely through reconstitution of the immune system. Post-AHSCT immune system showed a change in immune profile suggesting a shift toward tolerance characterized by depletion of pro-inflammatory TH1/17 cells, ageing of terminally differentiated effector memory cells, increase and in naive cells (Cencioni et al., 2022).

As of July 2019, 1446 Multiple Sclerosis (MS) patients were included in the European Bone Marrow Transplantation (EBMT) registry (Duarte et al., 2019; Sharrack et al., 2020). The EBMT autoimmune diseases working party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE) published a detailed review of the relevant evidence an comprehensive guidelines on the use of AHSCT in patients with MS (Sharrack et al., 2020). They recommend offering AHSCT for RRMS patients with high clinical and MRI inflammatory disease activity despite the use of one or more lines of approved DMTs, or treatment--naïve patients with aggressive disease, who develop severe disability in the previous 12 months. Evidence best supports treatment in patients who are able to ambulate independently (EDSS 5.5 or less), who are younger than 45 years and have disease duration less than 10 years (Duarte et al., 2019; Muraro et al., 2017a, 2017b; Alexander et al., 2018; Snowden et al., 2018; Das et al., 2019; Sormani et al., 2017; Burt et al., 2012; Mancardi et al., 2018; Cohen et al., 2019). Highly active RRMS failing at least one line of DMT may be considered for HSCT (Muraro et al., 2017b; Alexander et al., 2018; Das et al., 2019; Burt et al., 2019; Snowden et al., 2012; Alix et al., 2013). As for patients with SPMS or PPMS, they may be considered for AHSCT in the setting of evident inflammation (clinical relapses and gadolinium-enhancing or recent T2 lesions on MRI) (Sharrack et al., 2020). Finally, patients with pediatric onset MS (POMS) and breakthrough disease with less toxic treatments can also be considered for AHSCT (Sharrack et al., 2020).

Mariottini et al. compared retrospectively AHSCT with conventional DMT in RRMS patients following discontinuation of natalizumab: 3 years after natalizumab discontinuation, 54.5 % of patients who received AHSCT had no evidence of disease activity compared to 11.5 % of those who received DMT (Mariottini et al., 2019).

4.6.1. Recommendations

Consider offering AHSCT to:

- Patients with rapidly evolving aggressive MS and suboptimal response to one of the high efficacy medications
- Patients with highly active disease and suboptimal response to at least 2 high efficacy DMTs (third line rescue therapy)
- Patients with progressive Multiple Sclerosis (SPMS or PPMS) in the setting of active inflammation, either clinically or radiologically, and not responding to DMTs.

The selected patients should preferably be below the age of 50 years with EDSS ≤ 5.5 (ambulating independently) and disease duration less than 10 years.

4.7. Pregnancy and breastfeeding

Pregnancy is associated with significant hormonal changes that affect the immune system and therefore the clinical course of MS. A significant rise in serum levels of estradiol, estriol, progesterone and cortisol, leads to a shift in the balance from a pro-inflammatory to an anti-inflammatory state. Improvement in women counseling and the advent of high efficacy DMTs have increased the proportion of women with MS attempting to get pregnant. MS per se does not appear to carry a significant risk for an adverse pregnancy outcome compared with women without MS (Tsui and Lee, 2011). A meta-analysis of 22 studies reporting on 13,144 pregnancies, showed a slight increase in the rate of caesarian sections, abortions, low birth weight and prematurity but not to a concerning level (Finkelsztejn et al., 2011). The large prospective Pregnancy In Multiple Sclerosis (PRIMS) trial documented a 70 % decrease in relapse rate during pregnancy especially in the third trimester, followed by a rebound increase in relapse rate by 70 % compared to preconception (Confavreux et al., 1998). These findings were confirmed by more recent studies (Finkelsztejn et al., 2011; Hughes et al., 2014). In the era of new therapeutics, it appears that withdrawal of high efficacy DMTs prior to conception, especially lymphocyte trafficking agents, may result in relapse occurrence during pregnancy, mostly associated with prolonged washout periods

(Alroughani et al., 2018). In all studies, the pre-pregnancy ARR was the most important predictor of postpartum relapses, highlighting the importance of stabilizing the disease before attempting conception.

Despite more than 30 years of experience with DMTs in MS, we still lack controlled prospective studies that assess their safety during pregnancy. All DMTs might have potential adverse events on the fetus, and the general recommendation is to discontinue treatment before attempting conception. However, such approach will increase the risk of relapse especially if conception is delayed. In addition, there are concerns over potential risks of stopping a beneficial DMT during pregnancy in women with highly active disease. The use of IFNB and GA seems to be relatively safe during pregnancy based on large retrospective studies and pregnancy registries (Lu et al., 2012; Sandberg-Wollheim et al., 2018). Fingolimod and mitoxantrone have both been associated with congenital anomalies in humans and are thus contraindicated in pregnancy (Karlsson et al., 2014; Pozzilli et al., 2015). Teriflunomide was associated with embryotoxicity and teratogenicity in animal studies but data from clinical trials and post-marketing registries, did not show any increase in the rate of congenital anomalies or spontaneous abortions in 222 pregnancies with known outcomes (Vukusic et al., 2019). An interim analysis from the prospective, international DMF registry identified 345 pregnancies with exposure to the drug and known outcomes. The rate of spontaneous abortion was similar to the general population and there were no signs of increased rate of birth defects (Hellwig, 2022). Moreover, with a very short half-life of few hours, the drug is cleared from circulation within 24 h. Monoclonal antibodies such as natalizumab, alemtuzumab and the B cell depleting therapies do not cross the human placenta in significant amounts before week 20 of pregnancy. The Tysabri Pregnancy Exposure Registry (TPER) showed no significant adverse events in 355 prospectively followed pregnant women exposed to natalizumab (Friend et al., 2016). Natalizumab has been used up to the third trimester of pregnancy in patients with highly active disease, and induced only minor asymptomatic hematological abnormalities in the neonates (Haghikia et al., 2014). In a review of the alemtuzumab clinical development program, 233 pregnancies occurred in patients exposed to the drug, mostly 4 months after the last infusion (Oh et al., 2020). The rate of spontaneous abortion was similar to the general population and there were no signs of teratogenicity.

Women are generally advised to consider pregnancy after at least 1 year of disease remission irrespective of the DMT used. Although there are no recognized guidelines on when to discontinue DMTs for patients contemplating pregnancy, the panel reached a consensus on the washout periods based on the mechanism of action of the DMTs, regulatory recommendations and published studies and registries (Krysko et al., 2023; Cree, 2013; Bove et al., 2014). Interferons beta and glatiramer acetate may be continued till conception and during pregnancy as per their approved label. DMF can be continued until conception given its short half-life. On the other hand, it is recommended to continue natalizumab till conception and possibly till the end of the 2nd trimester if benefit outweighs risk given that those patients had highly active disease prior to natalizumab and are at risk of disease reactivation if discontinued. If patients are treated with immune reconstitution therapies such as alemtuzumab or cladribine, conception is recommended 4 and 6 months following the second course, respectively, in order to maximize treatment benefit while minimizing the risk of adverse events. Placental transfer of antithyroid antibodies and neonatal Graves' disease has been reported with alemtuzumab.

The average half-life of B cell depleting therapies ranges from 16 to 26 days, meaning they will be cleared from the maternal circulation before week 20 of gestation if administered before conception. Recent pregnancy registries have confirmed the safety of administering B cell depleting therapies just before conception (Das et al., 2018; Bove, 2023; Dobson, 2021) . On the other hand, their therapeutic effect outlasts their dosing interval, due to prolonged B cell depletion and delayed recovery of memory B cells compared to naïve B cells. Recent studies have actually shown very low relapse rates during pregnancy and postpartum period in patients receiving their last dose just before conception (Das et al., 2018; Smith, 2020; Kümpfel et al., 2021; Ciplea, 2020). Based on the accumulating evidence, attempting conception in the menstrual cycle following the last intravenous injection is gaining popularity. Due to the short half-life of ofatumumab (16 days), it can be discontinued once conception is confirmed.

Intravenous methylprednisolone is safe to treat relapses during pregnancy. Although its use during the first trimester was associated with cleft lip and palate, more recent studies did not find confirm such an association (Hviid and Molgaard-Nielsen, 2011). Although plasmapheresis has been used during pregnancy in severe relapses that showed no response to IV corticosteroids, the safety data is limited as the risks of hemodynamic instability and thrombophlebitis remain as potential concerns for its use (Cox et al., 2017). With respect to the use of MRI during pregnancy, a recent study reviewing 1737 pregnancies exposed to MRI during the 1st trimester did not reveal any increased risk to the fetus, but the administration of gadolinium contrast was associated with multiple complications including stillbirth (Ray et al., 2016).

The World Health Organization (WHO) recommends exclusive breastfeeding up to 6 months of age and continued breastfeeding with complementary food up to 2 years of age or beyond. In view of the significant health benefits of breastfeeding for both the mother and infant, patients with MS should be encouraged, not deprived, of breastfeeding. A protective effect of exclusive breastfeeding in the postpartum period was suggested by a study assessing 32 women with MS (Langer-Gould et al., 2009). A more recent systematic review and meta-analysis confirmed the association between exclusive breastfeeding and decreased postpartum relapse rate (Krysko et al., 2020). However, reverse causality remains a concern due to multiple confounding variables.

Only IFNB, GA and ofatumumab are approved for use during breastfeeding. Oral therapies have a low molecular weight and therefore, can be transferred into breastmilk. Breastfeeding should be avoided in patients on teriflunomide, S1P receptor modulators, DMF and cladribine. However, monoclonal antibodies are large molecules and therefore secreted in negligible amounts in breastmilk 1-week postdelivery (skipping the initial secretion of colostrum). Studies have shown that there were no significant adverse effects or negative impact on the development of infants of breastfeeding mothers exposed to natalizumab, ocrelizumab, ofatumumab or rituximab (Bove, 2023; Ciplea, 2020; Baker et al., 2015; Anderson, 2022; Bosshard et al., 2021; Chey and Kermode, 2022). Accordingly, breastfeeding should be considered in women on B cell depleting therapies, natalizumab or alemtuzumab. Breastfeeding should not be undertaken within four hours of B cell depleting therapy, alemtuzumab or IV-MP infusion.

4.8. Pediatric MS

Pediatric-onset MS, is generally defined as MS with onset before the age of 16 years (sometimes before the age of 18 years depending on the country's cutoff age). Between 3 and 10 % of patients with MS present under 16 years of age and <1 % under 10 years of age (Boiko et al., 2002).

Pediatric-onset MS patients have several distinctive clinical features compared to adult patients. They experience a more aggressive disease onset with disabling clinical symptoms, multifocal relapses and higher relapse rate early in the disease course (Banwell et al., 2007; Yeh et al., 2009). Around 98 % of POMS patients present with a relapsing remitting course, compared with 84 % of adult patients (Banwell et al., 2009). With respect to MRI findings, POMS patients tend to have a higher T2 lesion load; often located in the posterior fossa and spine with minimal disability and a tendency for lesions to disappear after therapy (Chitnis, 2006). Brain lesions in younger children (< 11 years) tend to be large with poorly defined borders and frequently confluent at disease onset (Callen et al., 2009).

Pediatric MS patients have slower disease progression over time but

reach disability milestones at younger age. In a large cohort from French and Belgian centers (Renoux et al., 2007), patients with pediatric MS reached the secondary progressive phase at ages approximately 10 years younger than patients with adult-onset disease, despite a slower rate of disability progression. The estimated median time between the first two neurologic episodes was 2.0 years (Renoux et al., 2007). The relatively slow development of irreversible physical disability in children is believed to result from better plasticity, allowing better recovery from relapses (Chitnis et al., 2011). Primary progressive course is rare in children and is often considered a red flag requiring additional work up.

Many diagnostic criteria for pediatric MS have been proposed. The criteria by the Pediatric International Study Group that were revised in 2013, have been applied in most studies (Krupp et al., 2013). The diagnosis of pediatric MS can be established by fulfilling one of the following criteria:

- $\geq$ 2 non-encephalopathic clinical CNS events with presumed inflammatory cause, separated by $>$ 30 days and involving more than one CNS area.
- One non-encephalopathic episode typical of MS which is associated with MRI findings consistent with 2017 Revised McDonald criteria for DIS and DIT criteria.
- One ADEM attack followed by a non-encephalopathic clinical event, three or more months after symptom onset, that is associated with new MRI lesions that fulfill 2010 Revised McDonald DIS criteria.

In children older than 12 years, a single first event (*e.g.* CIS) that does not meet ADEM criteria but fulfills the 2010 revised McDonald Criteria for DIS and DIT is enough to make the diagnosis of MS (Krupp et al., 2013). Generally, children are less likely to have intrathecal antibody production (OCBs or elevated IgG index) but show a high percentage of neutrophils in their CSF, suggesting prominent activation of the innate immune response (Peche et al., 2013).

The differential diagnosis of pediatric MS is broad. A comprehensive work up is recommended to exclude other mimickers especially in patients with atypical presentations or red flags. The differentials may include ADEM or neuromyelitis optica (NMO), vasculitis (*e.g.* systemic lupus erythematosus, Sjögren syndrome), hereditary (leukodystrophies and metabolic disorders), and vascular disorders (Rubin and Kuntz, 2013). A number of 'red flags' in the differential diagnosis of POMS have been suggested including encephalopathy and fever, progressive clinical course from onset, involvement of the peripheral nervous system or other organs, absence of CSF oligoclonal IgG, and markedly elevated CSF white blood cells and/or protein (Chitnis et al., 2011).

Given the relatively high relapse rate and accumulation of disability at younger age, early initiation of DMTs is advised to reduce the intense inflammatory process early in the disease (Chitnis et al., 2012). Postponing treatment can have a negative impact on social activities and academic performance. Initial evidence on the efficacy of DMTs in POMS was extrapolated from clinical trials in adults or based on observational or non-randomized prospective studies in pediatric cohorts evaluating primarily interferon beta and natalizumab. However, all DMTs approved for the adult population have been used in POMS and are likely to be efficacious.

Several Phase 3 randomized clinical trials in POMS have been conducted. The first approved DMT was fingolimod based on the results of the PARADIGMS study that evaluated the safety and efficacy of oral fingolimod *vs*. IFN-beta 1a in 215 children and adolescents over two years. Fingolimod showed a significant relative risk reduction of ARR by ~82 %, and 85.7 % of patients in the fingolimod group were free of confirmed relapses at month 24 vs. 38.8 % on IFN-beta 1a IM ($p < 0.001$) (Chitnis et al., 2018). Serious adverse events were higher in fingolimod arms (16.8 % *vs*. 6.5 %) and included seizures ($n = 4$), infections ($n = 4$), and leukopenia ($n = 2$).

TERIKIDS was a two-year, double-blind, placebo-controlled, trial of teriflunomide in 166 pediatrics patients randomized in 2:1 ratio (Chitnis et al., 2021). After 96 weeks, there was no difference in time to first confirmed clinical relapse with teriflunomide compared to placebo ($p = 0{\cdot}29$). The switch from double-blind to open-label treatment due to high MRI activity was more frequent than anticipated in the placebo group (26 % *vs* 13 %,), thereby decreasing study power and biasing the results against treatment efficacy. On the other hand, teriflunomide reduced the number of new or enlarged T2 lesions *versus* placebo by 55 % ($p = 0{\cdot}00{,}061$), and the number of gadolinium-enhancing lesions by 75 % ($p < 0{\cdot}0001$) (Chitnis et al., 2021). Upper respiratory tract infection, alopecia, paresthesia, and increased CK were more frequent in the teriflunomide arm. During the double-blind phase, four patients in the teriflunomide group had pancreatic adverse events of which three events led to treatment discontinuation (Chitnis et al., 2021). Teriflunomide was granted the EMA approval given the beneficial effects on radiological activities and the pre-specified sensitivity analysis that supports reducing the risk of focal inflammatory activity.

The CONNECT was an active-controlled, open-label, rater-blinded 96-week clinical trial in 150 patients with POMS randomized to DMF or IFN-beta1a IM (Vermersch et al., 2022). The primary end point was the proportion of patients with no new or newly enlarging T2 hyperintense lesions that was significantly higher in the DMF arm (16.1 % *vs* 4.9 %). The estimated proportion of patients who remained relapse free at week 96 was 66.2 % for DMF *vs* 52.3 % for IFN-beta1a. Adjusted ARR was 0.24 for DMF *vs* 0.53 for IFN-beta1a; the rate ratio for DMF *vs* IFN-beta1a was 0.46 ($p = 0.006$). Main adverse events were flushing and gastrointestinal upsets (Vermersch et al., 2022). To date, DMF is yet to receive regulatory approval. Other trials involving ocrelizumab (The US National Library of Medicine, 2023b), alemtuzumab (US National Library of Medicine, 2022), ofatumumab (US National Library of Medicine, 2021) and siponimod (US National Library of Medicine, 2021) are ongoing.

5. Conclusion

With evolving diagnostic criteria and the advent of new oral and parenteral therapies for MS, most current diagnostic and treatment algorithms need to be reevaluated and updated. Diagnostic and therapeutic decisions need to be made based on currently available scientific data as well as personal experience. The aim of this review is to provide recommendations and general guidelines for the diagnosis and treatment of MS based on scientific evidence and expert opinion.

CRediT authorship contribution statement

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Declaration of competing interest

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