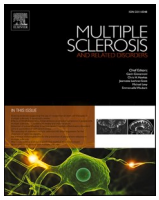
Multiple Sclerosis and Related Disorders 88 (2024) 105703

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Disease modifying treatment guidelines for multiple sclerosis in the United Arab Emirates

Anu Jacob [a,b,*], Ahmed Osman Shatila [c], Jihad Inshasi [d], Joelle Massouh [e], Ruquia Mir [f], Suzan Noori [g], Bassem Yamout [e,h], on Behalf of the UAE National Multiple Sclerosis Society

[a] Neurological Institute, Cleveland Clinic, Abu Dhabi, United Arab Emirates
[b] The Walton Centre, Liverpool, United Kingdom
[c] Department of Neurology, Sheikh Shakhbout Medical City Abu Dhabi, United Arab Emirates
[d] Department of Neurology, Rashid Hospital and Dubai Medical College, Dubai Health Authority, Dubai, United Arab Emirates
[e] Neurology Institute and Multiple Sclerosis Centre, Harley Street Medical centre, Abu Dhabi, United Arab Emirates
[f] Abu Dhabi stem Cell Clinic, United Arab Emirates
[g] University Hospital Sharjah, United Arab Emirates
[h] American University of Beirut, Lebanon

ARTICLE INFO

Keywords:
Multiple Sclerosis
Disease modifying treatment
National guideline
United Arab Emirates
Middle East
Gulf
UAE

ABSTRACT

The newly constituted National Multiple Sclerosis (MS) Society (NMSS)of the United Arab Emirates (UAE), set up a scientific committee to create a MS disease modifying treatment (DMT) guideline for UAE. The committee considered several unique features of the MS community in UAE including large number of expatriate population, wide variations in health insurance coverage, physician and patient preferences for DMT. The overall goal of the treatment guideline is to facilitate the most appropriate DMT to the widest number of patients. To this end it has adapted recommendations from various health systems and regulatory authorities into a pragmatic amalgamation of best practices from across the world. Importantly where data is unavailable or controversial, a common sense approach is taken rather than leave physicians and patients in limbo. The committee classifies MS into subcategories and suggests appropriate treatment choices. It recommends treatment of RIS and CIS with poor prognostic factors. It largely equates the efficacy and safety of DMT with similar mechanisms of action or drug classes e.g. ocrelizumab is similar to rituximab. It allows early switching of treatment for unambiguous disease activity and those with progression independent of relapses. Autologous hematopoietic stem cell transplantation can be offered to patients who fail one high efficacy DMT. Pragmatic guidance on switching and stopping DMT, DMT choices in pregnancy, lactation and pediatric MS have been included. It is expected that these guidelines will be updated periodically as new data becomes available.

1. Introduction

The United Arab Emirates (UAE) is home to about 10 million people, of which one million are Emirati citizens. UAE is considered a country with medium prevalence for Multiple Sclerosis (MS). Estimates of prevalence are crude and range from 57/100,000 increasing to 64/100,000 when age-standardised (Inshasi & Thakre, 2011, Schiess et al., 2016, Mohammed, 2016). MS is more common in native Emirati people than in a mixed population of Emiratis and expatriates with the majority having relapsing MS (Schiess et al., 2016).

All neurologists (not necessarily MS specialists) can manage MS. Primary care systems are not well established in UAE and patients self-refer to hospitals. Onward referrals to larger centres with expertise is uncommon, unless patients themselves chose to do so. Most MS Disease modifying treatments (DMT) are available in UAE. While UAE has a medical regulatory authority, its role has not yet extended into appraisals of individual medicines or cost effectiveness. Therefore, adoption of recommendations by the Food and Drug Administration(FDA) or European Medicines Agency (EMA) is the standard practice. There is presently no guideline for MS DMT in UAE. So, Neurologists use FDA, EMA approved drugs that are available in UAE as per their preferences and guided by the American Academy of Neurology (AAN), European Academy of Neurology (EAN) and Middle East North Africa Committee for Treatment and Research in MS (MENACTRIMS) guidelines (Yamout

* Corresponding Author: Anu Jacob. Neurological Institute, Cleveland Clinic, Abu Dhabi, PO box 112412, United Arab Emirates.
E-mail address: jacoba@clevelandclinicabudhabi.ae (A. Jacob).

https://doi.org/10.1016/j.msard.2024.105703
Received 21 January 2024; Received in revised form 13 May 2024; Accepted 4 June 2024
Available online 9 June 2024

et al., 2024). This pragmatic approach combined with affordability (UAE per capita GDP is 44,315 USD compared to the EU 38,411 USD) (GDP comparision UAE and EU) has helped the quick introduction of new drugs in UAE once approved in North America or Europe.

However, there are disadvantages to the use of "only approved treatments" approach. The health insurance coverage for many expatriates is limited and often excludes licenced MS DMTs due to high cost. Rituximab, a highly effective anti CD20 agent that is far cheaper and used widely in Scandinavian and other Arab countries is denied by insurers as it does not have a formal licence in MS. Early adoption of emerging treatments is limited. For example, autologous hematopoietic stem cell transplantation (AHSCT) used in Europe and USA for aggressive MS has just become available in UAE.

The newly constituted National MS Society (NMSS) of UAE, cognizant of the wide variations in health insurance coverage for the UAE resident population and the wide variations in patient and physician preferences, set up a task force to create a UAE MS guideline considering the several unique features of the MS ecosystem in UAE. The overall goal of the treatment guideline is to facilitate the most appropriate DMT to the widest number of patients. To this end it has adapted recommendations from various health systems and regulatory authorities into a pragmatic amalgamation of best practices from across the world (Yamout et al., 2024, Cross & Riley, 2022, Wiendl et al., 2021, Montalban et al., 2018,9, Chitnis et al., 2018, Rae-Grant et al., 2018, Claflin et al., 2019, Simonsen et al., 2021, National MS Society USA 2023, NHS England 2019, Yamout et al., 2020). Importantly where data is unavailable or controversial, a common sense approach is taken rather than leave physicians and patients in limbo. This guideline is not intended to be an exhaustive review of MS or the individual drugs and their data on safety or efficacy. It also does not cover symptomatic treatments, rehabilitation or disorders other than multiple sclerosis.

The version of guidelines agreed by the authors were reviewed by 15 UAE neurologists with expertise in MS (see acknowledgements) and their suggestions incorporated where possible to form the final version. It is expected that these guidelines will be updated periodically as new data becomes available.

2. Diagnosis of MS

MS is an immune mediated disease of the central nervous system, and the most common cause of nontraumatic neurological disability amongst adults. It is a chronic lifelong disease in most affected people. The disease severity is variable, and periods of remission and stability occur. In general, once initiated, MS continues to progress driven by multiple mechanisms, and majority of untreated patients will develop disability after 20 years. These premises and the absence of a diagnostic test has led to the long-held convention of basing the diagnosis on dissemination in space (multiple areas in the CNS) and time (chronicity) and exclusion of alternative diagnoses where appropriate. Diagnostic criteria for MS have gone through several iterations, the most recent being the Modified McDonald's criteria 2017. MS can also be classified into the following phenotypes: Radiologically isolated syndrome (RIS) (De Stefano et al., 2018, Okuda et al., 2009, Lebrun-Frénay et al., 2023), Clinically isolated syndrome (CIS), Relapsing Remitting MS (RRMS) and Progressive MS which can be primary progressive (PPMS) or secondary progressive (SPMS) (Lublin et al., 2014) (Table 1 panel 1). This traditional and arbitrary boundary between relapsing and progressive MS were set to facilitate treatment trials in MS which it served well. These boundaries have blurred in recent years. The disease is now considered biologically (even if not clinically) progressive from the beginning with evidence of axonal loss from the onset albeit at variable rates. Inflammatory activity is predominant early on and waning with time. The recently proposed concept of Progression Independent of Relapse Activity (PIRA) may account for most of the disability seen early in the disease (Cree et al., 2019, Kappos et al., 2020). The committee recommends using standardized MRI protocols for diagnosis and follow up of patients with MS according to the 2021 Magnetic Resonance Imaging In Multiple Sclerosis (MAGNIMS) consensus recommendations (Wattjes et al., 2021).

Table 1
Panel A. Traditional subtypes of MS. Panel B. Poor prognostic factors in MS. Panel C. RRMS subcategories based on poor prognostic factors. Adapted from multiple sources.

A. **MS Phenotypes**	
Radiologically isolated syndrome (RIS).	The presence of asymptomatic, incidentally identified demyelinating-appearing white matter lesions in the central nervous system (Okuda criteria) within individuals lacking symptoms typical of multiple sclerosis.
Clinically isolated syndrome (CIS).	A single or first episode of demyelination consistent with MS but does not yet fulfill McDonald diagnostic criteria. Up to 80% of CIS convert to MS in 20 years. Those with MRI changes have a higher risk.
Relapsing Remitting MS (RRMS).	See section below
Progressive MS	Course characterised steadily increasing objectively documented neurological disability independent of relapses. **Primary progressive multiple sclerosis** (a progressive course from disease onset) and **secondary progressive multiple sclerosis** (a progressive course following an initial relapsing-remitting course). These progressive categories can be active (relapses or MRI evidence of inflammatory change) or inactive.
B.**Poor prognostic factors in relapsing MS**	
High relapse frequency in the previous year (≥2 relapses)	
Relapse severity (pyramidal/cerebellar systems involvement)	
Incomplete recovery from relapses	
High T2 lesion load on MRI	
Spinal or infratentorial lesions	
Multiple gadolinium enhancing lesions	
T1 black holes and brain atrophy (less reliable markers)	
C.**RRMS subcategories based on prognostic factors**	
1. Rapidly Evolving Severe (RESMS)	2 or more disabling relapses in previous year with incomplete recovery and with 1 or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI
2. Highly Active MS (HAMS)	1 relapse in the previous year and MRI evidence of disease activity with at least one associated poor prognostic factor
3. Moderately Active MS (MAMS)	Clinical or MRI evidence of new disease activity in the previous year but without any poor prognostic factor as above
4. Low Activity MS (LAMS)	Relapsing MS *not on treatment* and yet do not show evidence of new disease activity (no relapses, MRI changes or progression) for > 1 year or disease activity level is less than that seen in moderately active MS.

3. Defining RRMS severity and categories

Several poor prognostic factors have been identified and using those with higher predictive values (see Table 1 panel 2) attempts have been made to classify RRMS into subcategories (NICE Technology appraisal guidance [TA616] 2019, NHS England 2019). The committee preferred to adopt already established definitions (even if imperfect) where possible rather than create new definitions to avoid confusion. These subcategories are Rapidly Evolving Severe (RES) MS (Kappos, 2020; Wattjes, 2021, Yamout et al., 2024, NHS England 2019), Highly active MS (HAMS) (Kappos et al., 2020, Yamout et al., 2024, NICE Technology appraisal guidance [TA616] 2019), Moderately active MS (MAMS) (Yamout et al., 2024) and Low activity MS (LAMS) with no recent disease activity or activity less than that in moderately active MS (Ramo-Tello, 2014; AAN; NICE Technology appraisal guidance [TA616] 2019; NHS England 2019) (See Table 1 panel 3).

4. Treatment of acute attacks of MS

Corticosteroids have been the gold standard for treatment of acute attacks of demyelination including MS and is supported by several studies (Ramo-Tello et al., 2014, Barnes et al., 1997, Burton et al., 2009, Citterio et al., 2000). Typical doses include intravenous methyl prednisolone (IVMP) 0.5-1 g IV for 3-5 days.

Oral methyl prednisone (500-1000 mg daily for 3- 5 days) or oral prednisolone 1250 mg has similar benefits but may have more side effects (Ramo-Tello et al., 2014, Burton et al., 2009, Morrow et al., 2004, Liu et al., 2017).

The need for oral prednisone tapering after IVMP should be considered on an individual basis in patients with severe attacks or those considered to be at an increased risk of rebound as there is insufficient evidence for routine use in all relapses (Perumal et al., 2008, Bazi et al., 2021).

Plasmapheresis is recommended in patients with severe relapses who fail to respond to high dose steroids though the threshold of what is severe is still undefined (Cortese et al., 2011, Weinshenker, 2001, Weiner et al., 1989). The panel recommends early use of plasmapheresis, particularly in relapses affecting the brainstem, spinal cord or optic nerves to hasten recovery and preserve neurological reserve. A second course of high dose IVMP can be used if plasma exchange is not possible, or recovery remains poor. IVIG has not been shown to have a beneficial role in MS relapses and is limited to situations where corticosteroids or PLEX are not available or contraindicated (Visser et al., 2004).

5. Overview of DMT and consensus statements

Over the last 30 years more than 20 drugs with effect on relapses and progression have been developed. To aid clinical practice, the committee agreed on a pictorial representation of relative efficacy and safety (Fig. 1) and two treatment algorithms (Figs. 2 and 3). This is based on wide literature review, international guidelines, expert recommendations and personal experience (Cross & Riley, 2022, Wiendl et al., 2021, Montalban et al., 2018, 9, Chitnis et al., 2018, Rae-Grant et al., 2018, Claflin et al., 2019, Simonsen et al., 2021, National MS Society USA 2023, NHS England 2019, Yamout et al., 2020).

The committee also agreed on the following 25 consensus statements on DMTs to guide recommendations.

1. MS is a chronic immune mediated disease with a relapsing remitting followed by progressive course in the majority and a progressive course from the beginning in some.
2. The underlying pathogenesis is inflammation and degeneration. They might be independent of each other to some degree, but ongoing inflammation predisposes to early degenerative changes, manifesting clinically as progression.
3. The progressive stage of the disease without evident inflammation has limited treatment options.
4. The therapeutic window of opportunity is early in the course of the disease which narrows with duration of disease and age.
5. While high-quality evidence is desirable in supporting all recommendations it may not be always available.
6. It is in general true that DMT that are more effective in controlling relapses also have more impact on delaying progression. Since long term (> 15 years) data on most DMT are unavailable, at present one can only extrapolate that short term benefits will have long term impacts.
7. There are many uncertainties about the best way to treat MS and while more evidence may become available in the future, a pragmatic common sense approach has to be taken at present where evidence is lacking.
8. Patient preferences regarding frequency, route of administration (oral, intravenous, subcutaneous) and location (in-hospital versus home) will influence treatment decisions and should always be taken into consideration.
9. Physicians should clearly educate patients about the risk of disease progression and disability and relative efficacies of individual drugs /drug categories on disease control in terms of new attacks, brain lesions and progression.
10. Licensed DMT are expensive and may not be available for all persons with MS.
11. Pharmaceutical companies must provide patient support programs to those who are uninsured.
12. Use of off-label licensed medications is justified to treat MS in resource poor settings when alternative approved treatment options are unavailable or unaffordable (Laurson-Doube et al., 2021).

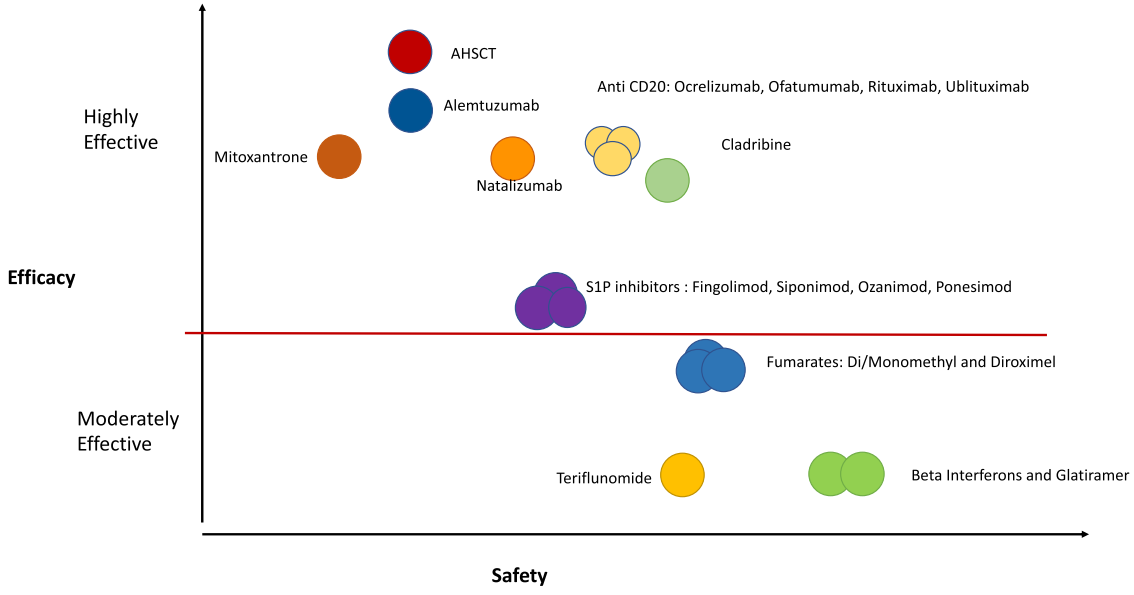


Fig 1. The authors' personal and simplified overview of MS DMT in terms of relative efficacy versus safety. While less quantifiable, perceived 'safety' incorporates serious and potentially fatal adverse effects including teratogenicity, PML, major infections, cardiovascular complications, emergence of autoimmunity or immune reconstitution inflammatory syndrome (IRIS), vaccine responsiveness and secondary cancers.

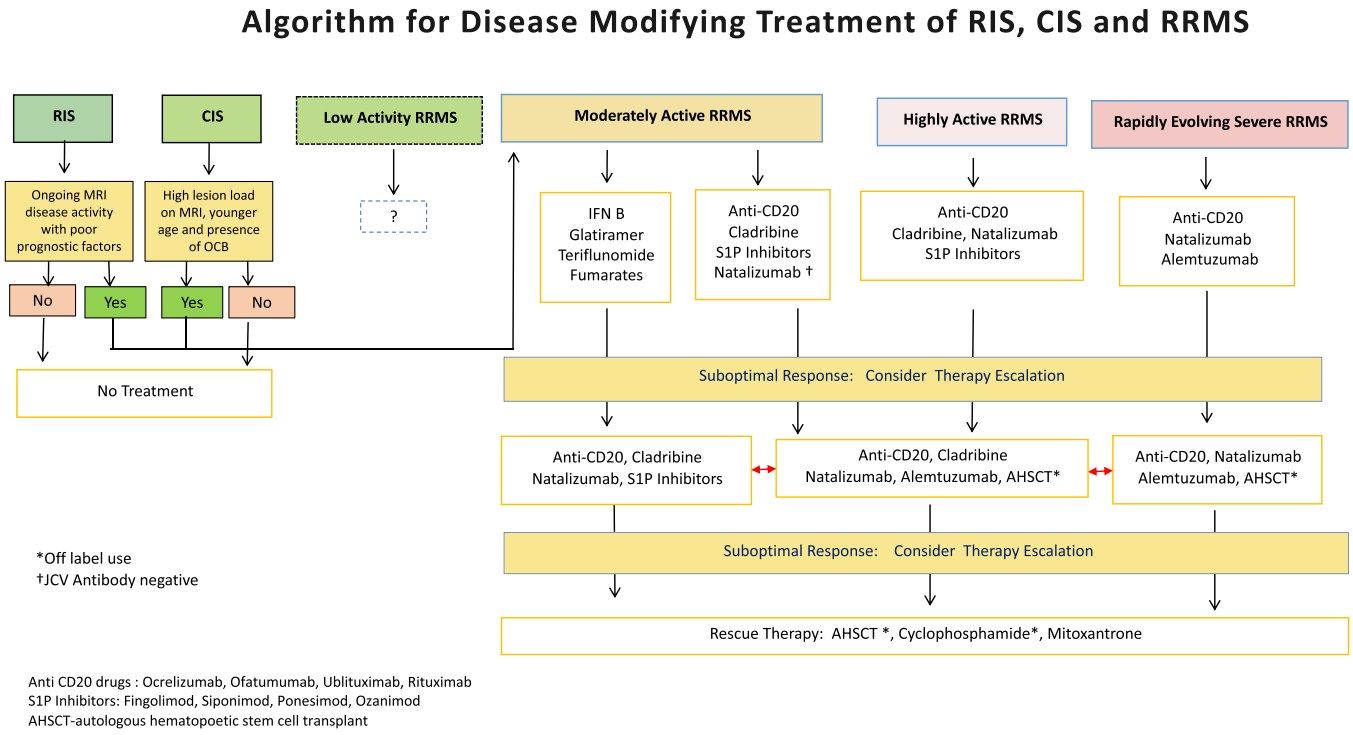


Fig. 2. Algorithm of DMT use in RIS, CIS and relapsing MS . Refer to text for details and classification of RRMS severity and poor prognostic factors. Suboptimal response includes relapse and MRI new lesion formation or lesion enlargement. Progression independent of relapses can also be considered reason to switch though evidence is limited. Low activity RRMS may or may not be treated and depends on an informed patient and physician discussion. See text for further discussion. RIS – radiologically isolated syndrome. CIS – clinically isolated syndrome. AHSCT – autologous hematopoietic stem cell transplant.

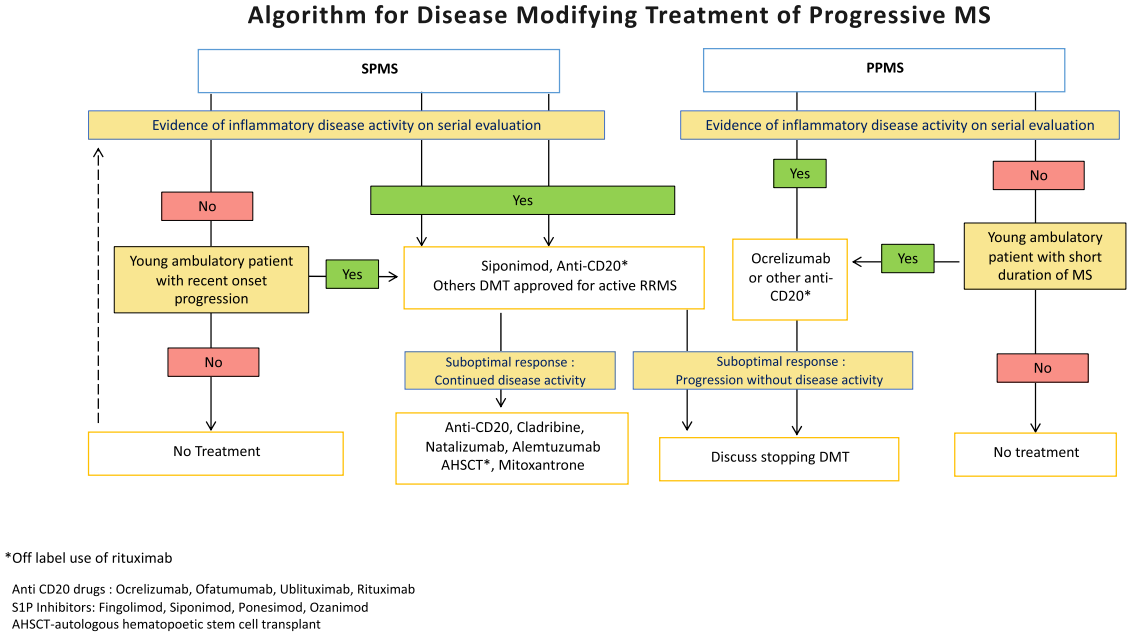


Fig 3. Treatment algorithm for progressive MS. Suboptimal response includes relapse and MRI new lesion formation or lesion enlargement. SPMS – secondary progressive MS, PPMS- primary progressive MS. AHSCT- Autologous hematopoietic stem cell transplant

13. The authors have attempted to stratify DMTs (Fig. 1) on the basis of their efficacy in controlling relapses versus overall safety, although no head to head controlled trials are available for many of them, especially the high efficacy DMT. While the positions of DMTs at the ends of the spectrum e.g. interferons (low risk) and mitoxantrone (high risk) are uncontroversial, we appreciate that that the relative positions of the drugs in between can be controversial and arbitrary. Nevertheless, some order has to be made to facilitate decision making amidst a plethora of drugs. Teratogenicity, progressive multifocal leukoenecpahlopathy (PML), other serious infections, cardiovascular complications, emergence of autoimmunity or immune reconstitution inflammatory syndrome (IRIS), vaccine responsiveness and secondary cancers have been our main considerations. Each deserves its own

scale but that would be very confusing. Hence, we chose this pragmatic representation that is agreeable to the authors and experts.

14. MS DMT can be grouped as
    a. Moderately effective : Interferons, Glatiramer, Teriflunomide, Fumarates
    b. Highly effective : S1P inhibitors, Cladribine, antiCD20 drugs, Mitoxantrone, Natalizumab, Alemtuzumab and AHSCT (off label)
15. Individual drugs within a class of DMT may have comparable levels of efficacy. e.g. ocrelizumab and rituximab
16. Rituximab though unlicensed for MS by EMA and FDA, was recently added by the World Health Organization (WHO) to its Essential Medicine List for MS (World Health Organization 2023) and is widely used in Scandinavian and Arab countries. It can be used when licenced high efficacy medications are unavailable or unaffordable (see section on off label use) (Yamout et al., 2018, Zeineddine & Yamout, 2020).
17. Though licenced, mitoxantrone should be used only in exceptional circumstances due to their side effect profile.
18. Azathioprine and Mycophenolate are unlicensed for MS and not first choices as MS DMT. But they do have varying levels of efficacy and may be treatment options when licensed DMT are unavailable or unaffordable (see section on off label use)
19. AHSCT is likely the most effective DMT but lacks highest level of evidence at present. It can be offered to active RRMS or progressive MS in select situations (See section on AHSCT and algorithms)
20. The traditional view of MS treatment has been one of caution i.e. using higher efficacy medications only when lower efficacy medications did not control the disease – the 'escalation' approach. Long term safety concerns where the important reason for this approach. However this approach has been criticised justifiably for the following reasons
    - Benign MS may not be truly benign in the majority of cases and can only be diagnosed retrospectively
    - It is not possible to predict reliably long term outcomes at onset, although many clinical, radiological and laboratory factors may indicate the long term trajectory in individual patients (Kappos et al., 2020).
    - Significant number of patients will not achieve disease control and will switch to a high efficacy agent in time.
    - Time lost is not regained.
    - Progression and disability accumulation happen earlier in those on lower efficacy medications
    - While the notion that "high efficacy DMTs cause more life threatening side effects", was applicable in the era of cyclophosphamide, mitoxantrone and natalizumab (before PML de-risking strategies), that is not true with commonly used current DMTs. Even for those drugs with the potential for long term side effects, de-risking approaches can effectively reduce harm e.g. JCV index monitoring and extended interval dosing for natalizumab.
    - Thus the induction approach of using higher efficacy drugs from the beginning is justifiable in many cases
21. Defining MS stage and severity is helpful in deciding the drug of choice
22. The goal of treatment with DMT is to achieve no evidence of disease activity status (NEDA) typically, the absence of relapses, progression, and MRI changes.
23. Evidence of significant continued disease activity is a reason to switch treatment
24. Pregnancy, breast feeding and paediatric MS have unique considerations
25. Vaccinations are advised before starting immunosuppressive DMT as per several international guidelines (Farez et al., 2019, Otero-Romero et al., 2023).

6. DMT recommendations

6.1. Radiologically isolated syndrome of demyelination

No drug is currently approved to treat RIS. Therefore, it is even more important that careful and detailed questioning of prior symptoms that may clinch the diagnosis of MS is made. Family members or past physicians should be contacted for accurate information and documentation obtained from other hospitals. Up to 30% of patients thought to be asymptomatic have had previous symptoms suggestive of demyelination (Gout et al., 2011).

10-year follow-up of patients with RIS have shown that 51% of patients develop a clinical event. Four independent risk factors- younger age, oligoclonal bands in CSF, infratentorial and spinal cord lesions and gadolinium enhancing lesions were independent predictors of clinical conversion. One factor alone increased risk by 29% and all four by 87% (Lebrun-Frenay et al., 2020).

Some patients demonstrate significant new subclinical disease activity on serial MRIs. In the ARISE double blind RCT of 87 RIS patients randomized 1:1 between dimethyl fumarate and placebo, 7% patients in placebo and 3% in dimethyl fumarate group developed a clinical event (87% risk reduction) at 4 years (Okuda et al., 2023). In the Teriflunomide in RIS trial, 18% of patients (8/44) in the treatment arm and 44% patients (20/45) in the placebo arm developed a clinical event at 3 years (risk reduction of 72%) (Lebrun-Frénay et al., 2023). Based on these data the committee feels that it is reasonable to treat preemptively those cases of RIS with high risk of conversion to clinical MS. This decision may not be easy to make and a second opinion from experienced MS neurologists or centers is advised.

Recommendation:

- ***Patients with RIS should be referred to a specialized MS centre for further management.***
- ***Patients with predictors for clinical conversion and unambiguous new radiological disease activity on MRI, should be considered for treatment with DMT or followed up carefully.***

6.2. Clinically isolated syndrome of demyelination

A single or first episode of demyelination consistent with MS but not yet fulfilling the 2017 Mc Donald criteria is labelled as CIS. Up to 80% of CIS convert to MS within 20 years. Those with MRI lesions have a higher risk (Fisniku et al., 2008).

The definition of CIS in the 2010 Mc Donald criteria included those with enhancing lesions on MRI and oligoclonal bands in the CSF. However, in the 2017 MS criteria such patients were diagnosed as MS. Consequently, the number of patients diagnosable with CIS nowadays has decreased significantly.

The decision to treat such CIS patients i.e. with MRI suggestive of demyelination but without activity (no new MRI lesions or Gd enhancement) or CSF oligoclonal bands must be weighed carefully as some patients may never develop further lesions that confirm MS. While some countries support treatment (AAN) some do not or limit treatment options (IFN or GA in EAN 2017 guideline (Montalban et al., 2018), no treatment in NHS England 2019 guideline (NHS England 2019).

Recommendation

- ***Patients with CIS should have a thorough review of the diagnosis to rule out alternative diagnoses.***
- ***In case such work-up is negative and the overall clinical and radiological picture is predictive of future development of MS, treatment can be offered.***

- ***Patients with CIS and high MRI lesion load (> 9 T2 lesions), and/or severe first attack with incomplete recovery, can be treated.***
- ***If treatment for CIS is delayed, clinical and radiological follow-up including a yearly MRI is recommended.***

6.3. Relapsing remitting MS

More than 20 drugs are available to treat RRMS with varying efficacy and risks. Information on these is now well entrenched in literature. The details of the pivotal trials are outside the scope of this document. RRMS is subclassified into 4 categories based on degree of disease activity and prognostic markers as outlined in Table 1. Rapidly evolving severe MS (RESMS), Highly active MS (HAMS), Moderately active MS (MAMS) and RRMS with no recent disease activity or activity less than that seen in moderately active MS.

Treatment initiation and switching in RRMS.

- There is very little head-to-head data comparing various DMTs to propose a fully evidence-based algorithm. Yet one is needed to assist the clinician in daily practice. Using our assessment of relative efficacy and safety we have used consensus and peer review among UAE expert physicians to suggest a pathway. Based on the sum of available knowledge the following recommendations are made (Fig. 2).
- Rapidly evolving severe MS (RESMS)

  The initial choice of DMT reflects the severity of disease and the need to control inflammatory activity quickly. Thus, RESMS is treated with highly effective and quick acting DMTs i.e anti CD20, natalizumab or alemtuzumab. Ongoing disease activity after adequate period on treatment is uncommon. Lateral switching between the 3 options or AHSCT is the next step. The need for cyclophosphamide or mitoxantrone is rare but remains an option.
- Highly Active MS The initial treatment is similar to RESMS with first line DMT including cladribine or S1P inhibitors which have a slower onset of action but excludes alemtuzumab due to its adverse side effects. For those with continuing disease activity, switch between the above (excluding S1P inhibitors) and consider alemtuzumab.
- Moderately active MS All DMTS with the exception of alemtuzumab (considering potential side effects) can be used. Typical patients are those with a recent diagnosis or anxious and unsure about treatments and have low disease activity (including patients with RIS or CIS qualifying for treatment). We recognise that many patients in this group will prefer perceived safety over efficacy, and we have created two treatment streams - one that uses 'safe but less effective" and other with "less safe but more effective". Escalation depends on the initial choice and degree of disease activity. Subsequent florid MRI changes or disabling relapses clearly warrant high efficacy treatments as indicated but patients with minor events may prefer to go on to "gentler agents" in keeping with our general impression of efficacy as in Fig. 1
- Low activity MS.
  - These are patients who are not on treatment and haven't had any recent (>1 year) clinical or MRI disease activity. Thus, they are apparently 'stable' even after a fulminant onset in the past. Traditionally such patients were labelled 'inactive MS or benign ' and not treated and many may remain stable for indefinite periods. The realization that at least a proportion of these become active in the future or progress independent of relapse activity (PIRA) / have 'smoldering MS' has led to hesitation in using those terms here. While it certainly is inappropriate to treat all patients with low or absent disease activity it's uncertain whom to treat if any. Many guidelines do not discuss this patient group. We acknowledge their existence and have indicated the uncertainty regards treatments in the algorithm and suggest referral to expert centers to decide on a case-by-case basis.
- Rituximab can be used (off label) for all levels of activity where other appropriate options are either unavailable or unaffordable (see section on rituximab later)
- Switching from DMTS that have had adequate dose and time to act (typically 6 months) is usually straight forward. But alemtuzumab and cladribine need at least 2 courses (given 12 months apart) to be effective and may remain effective for long. Therefore, it is reasonable to tolerate minor disease activity on these two drugs until 6 months after second year's dose is completed). Persisting disease activity beyond that justifies a switch if the patient and physician deem appropriate, particularly if there are many other effective drugs available. Alternatively, a third course of alemtuzumab or cladribine can be considered if the breakthrough activity is mild.

Recommendations

- ***All RRMS patients with active disease (RES, highly active, moderately active) are recommended DMT***
- ***For RES MS high efficacy DMT are recommended***
- ***For highly active RRMS high efficacy DMT are recommended***
- ***For moderately active RRMS both high and moderate efficacy DMT can be used***
- ***Treatment should be escalated in the presence of ongoing disease activity determined clinically or radiologically.***
- ***Patients with RRMS opting not to be on treatment should be monitored clinically and radiologically 6-12 monthly.***
- ***The decision to treat or not treat Low activity RRMS is controversial and can be individualized. When there is doubt a second opinion from an expert center is recommended.***

6.4. Secondary progressive MS

The first drug to show benefit in SPMS was mitoxantrone and was approved by FDA in 2000 (Hartung et al., 2002). In subsequent years many of the DMTs that were effective in relapsing MS did not show benefit in SPMS trials. On post hoc analysis, though overall negative, many of them seemed to influence the subgroup of patients with disease activity. In 2019 a trial of Siponimod met its primary and point and was approved for active SPMS (Kappos et al., 2018). 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. In addition, all patients recruited were below 60 years with an EDSS of 6.5 or less (not wheelchair-bound). FDA then approved cladribine (Rice et al., 2000, Beutler et al., 1996, FDA 2019) and then in a sweeping move widened the licence of all approved DMTs to include active SPMS (Cree et al., 2021, Hollen et al., 2020, Eckert et al., 2020) (Table 2). This change acknowledged that MS disease state is a continuum and ongoing inflammatory activity should be treated irrespective of the clinically defined artificial stage of the disease. The prevailing wisdom is that drugs that suppress inflammatory activity in the 'relapsing stage' will be effective for inflammatory activity in the 'progressive' stage too.

Treatment naïve SPMS patients are typically begun on Siponimod or anti CD20 agents (though any drug used in RRMS can be used as per FDA). Break through disease activity in the form of new MRI lesions and relapses warrants escalation to anti CD20 agents, cladribine, natalizumab, alemtuzumab, AHSCT or mitoxantrone. If progression continues without new MRI lesions and relapses, a candid discussion about discontinuation of treatment is required as outlined later.

The evidence for using DMT in SPMS without evidence of inflammatory activity is scarce. For young patients with recent onset secondary progressive MS treatment with Siponimod or anti CD20 medications is reasonable (Yamout et al., 2024, ECTRIMS & EAN 2021). If patients already on a DMT transition into SPMS it is reasonable to switch from the existing DMT to one that has an alternate mechanism of action with established evidence in SPMS. If progression continues without evidence of new inflammatory activity, discontinuation of treatment should be

Table 2
DMT licensed for Progressive MS (SPMS and PPMS). CDP- confirmed disability progression

DMT in Progressive MS				
Drugs approved for SPMS	Indications	Agency	Year	Comments
Siponimod	Active SPMS	FDA EMA	2019	EXPAND was the first large RCT in SPMS to have met the primary end point. Lower number of patients with CDP at 12 weeks of 26% vs 32% (ARR 6%). Benefit seen only in active disease (Kappos et al., 2018).
Interferon beta 1a and Ib, Glatiramer acetate, Teriflunomide, Di, Monomethyl and Diroximel fumarate, Fingolimod, Ozanimod Ponesimod, Natalizumab, Ocrelizumab, Ofatumumab, Cladribine, Alemtuzumab	Active SPMS	FDA	2019 (FDA)	Retroactive approval based on trials in RRRMS. Cladribine and Alemtuzumab are approved to use only after suboptimal response to at least one DMT
Mitoxantrone	SPMS Progressive relapsing, or worsening relapsing-RRMS		2009	Lifetime dose is limited to 140 mg/m^2 Rarely used nowadays due to risk of cardiomyopathy (2.6%) and leukemia (0.8%)
Drugs approved for PPMS				
Ocrelizumab	PPMS	FDA, EMA	2017	ORATARIO Trial 12 -week CDP 33% vs 39% in placebo (Montalban et al., 2017)

considered.

Recommendations

- ***SPMS with active disease, defined as presence of relapses or enhancinglesions on MRI, should be treated with DMT.***
- ***In young patients without evidence of disease activity in whom progression started recently, treatment may be initiated with / switched to, Siponimod or anti CD20 medications.***

6.5. Primary progressive MS

The only DMT of proven benefit in PPMS is ocrelizumab (Montalban et al., 2017) (Table 2). Though numerous other DMTs have been trialed, none have shown conclusive benefit. The ocrelizumab treated patients in ORATARIO trial were ≤ 55-year-old, with a disease duration ≤ 15 years and an EDSS ≤ 6.5. The treatment effect seems to be driven primarily by patients who had Gd+ lesions at baseline. Surprisingly rituximab an antiCD20 with very similar biological effects did not show benefits in the Olympus trial possibly probably due to older age and longer disease duration of patients (mean age 44.7 vs 50.1years; mean disease duration 2.9 vs 4.1 years) (Hawker et al., 2009). The panel also considered that a chronological age based cut off useful in clinical trials may not be appropriate in clinical practice and has extended the upper age limit to 60 years to account for biological variability.

Recommendation:

- ***Patients with PPMS, age ≤ 60 years, EDSS ≤ 6.5 (i.e. not wheelchair bound) and disease duration ≤ 15 years can be treated with ocrelizumab. In keeping with the pragmatic nature of this guideline, the panel proposes that where Ocrelizumab is inaccessible, rituximab or other B-cell depleting therapies can used.***
- ***Treatment escalation in PPMS patients on ocrelizumab/other anti CD20 is not commonly done. If there is indeed new lesion development on serial scans, careful exclusion of other causes (small vessel ischemia disease) and referral to expert centers is advised.***
- ***If there is progression without new lesion development, then similar to SPMS, DMTs have not shown to be effective, and discontinuation of treatment should be considered.***

7. Switching DMT

- **Treatment escalation due to continuing inflammatory activity.**
  Presence of unequivocal continuing disease activity (clinical relapses, or radiological activity i.e., gadolinium enhancement or new/enlarging T2 lesions) after being on a DMT for sufficient period of time and on an appropriate dose to be effective (at least 6 months) is sufficient indication to switch if patient and physician deem appropriate. When there is doubt on the nature of new MRI lesions (small vessel ischemia or nonspecific lesion versus demyelination) we suggest stricter criteria of 2 new/enlarging lesions and at least 1 year on DMT. Typically switching should be to a DMT with alternate mechanism and higher efficacy.
- **Switching for progression independent of relapses (PIRA).**
  The panel felt that switching can be done for PIRA though there is only limited evidence to guide DMT in this state (Maarouf et al., 2024). The general principles outlined earlier apply. i.e. the newer DMT should be an alternate mechanism and preferably higher efficacy. There is no universally accepted definition for PIRA (Sharrad et al., 2023, Ontaneda et al., 2023), but we find a recent proposal agreeable i.e. 'a person with relapsing MS with baseline EDSS ≤ 4.5 (to exclude most SPMS), experiences a worsening of disability (EDSS change of ≥ 1.5 (if baseline EDSS 0) or ≥1 (for baseline EDSS between 1-4.5) that is sustained over 3- 6 months. There should not be a relapse in the preceding 90 days or succeeding 30 days (Sharrad et al., 2023).
- **Switching for other reasons**
- Switching maybe considered due to intolerable side effects (clinical or laboratory abnormalities) burdensome modes of administration, anxiety about potential side effects e.g. switch from natalizumab with high JCV index or poor adherence (Yamout et al., 2024, 64).
- Sometimes side effects can be mitigated by dose reduction (interferons, azathioprine, teriflunomide) or extended intervals (natalizumab), while maintaining efficacy.
- Neutralising antibodies against interferons and natalizumab can reduce efficacy and can be an indication to switch.
- Switching from natalizumab or S1P inhibitors can lead to rebound disease activity (activity worse than baseline).
- Switching is also needed for pregnancy planning (see section on pregnancy and lactation).
- Switching maybe required due to unaffordability. Patients with highly active disease who are on a highly effective DMT should opt for a highly effective DMT even if unlicenced. e.g., switching from ocrelizumab or natalizumab to rituximab rather than interferons or teriflunomide.

8. Additional DMT in resource limited settings

Many medications that had positive results in initial trials were not evaluated in phase 3 trials nor were licenses sought presumably because

of the parent company's strategic business decisions. An example is rituximab. Despite showing highly positive results in the HERMES trial (Hauser et al., 2008) in relapsing MS, phase 3 trials were not done presumably since rituximab was soon to come off patent. Instead ocrelizumab was developed which still has another decade on patent. Up to 80% of patients with MS who remain untreated will develop a progressive course with time. MS societies and neurology associations recommend the use of DMT in all patients who have active MS. However, DMT are expensive. Even in resource rich UAE, there is a significant proportion of uninsured or inadequately insured expatriates. The high cost licensed DMTS are often not covered, or co-pays are unaffordable. Considering that 90% of the UAE population are expatriates, it could mean that a significant number of MS patients in UAE may not be able to access effective DMT. There is thus the need to facilitate low cost but effective off label DMT. The most recent World Health Organization Essential medicines list has included 3 MS drugs – rituximab, cladribine and glatiramer acetate. All 3 drugs have a valuable position in treating MS in UAE and are included in this guideline. The committee therefore fully endorses the WHO recommendation and supports its adoption in UAE (World Health Organization 2023). Table 3 summarizes DMT that are unlicensed but have reasonable evidence of effectiveness.

Recommendation

- ***Amongst the many off label treatments rituximab is the most effective and can be substituted for licensed anti-CD20s ocrelizumab, ofatumumab and ublituximab***
- ***Azathioprine is an option for milder forms of active MS, with less robust data***
- ***Mitoxantrone and cyclophosphamide are effective in aggressive forms of MS and can be used for a limited period and within the allowed cumulative dose.***
- ***Off-label DMT should only be used in low-resource settings when labelled equivalent DMTS are either unavailable or unaffordable.***

9. Autologous hematopoietic stem cell transplantation

Ablation of the immune system with high dose chemotherapy followed by autologous hematopoietic stem cell transplantation (AHSCT) for the treatment of MS has been explored since the first report in 1997 (Fassas et al., 1997). It can be a once-only treatment with therapeutic effect lasting many years, the closest result to a cure to date . Other DMT can be stopped thus avoiding cumulative side effects. It can also be a cost saving opportunity – the cost of a single treatment can offer several years of sustained remission compared with continuous treatment with DMTs (Burt et al., 2020).

While AHSCT is an exciting treatment option, it has not yet received FDA or EMA approval. Several trials comparing AHSCT to best available medical treatment are recruiting and are expected to report their results in next few years. Several case series, uncontrolled phase 2 clinical trials, and small randomized clinical trials have demonstrated the efficacy of AHSCT in patients with active relapsing MS, including marked reduction in relapses, MRI lesion activity, and brain volume loss (albeit after initial acceleration).

A cross-sectional analysis reveals that the proportion for whom NEDA was achieved at 2 years was 70-92% compared to 15-50% with DMT (Muraro et al., 2017, Sormani et al., 2017[a], Sormani et al., 2017[b]). Disease control is often durable, lasting up to 15 years or more without the need for ongoing DMT in many patients (Muraro et al., 2017). NEDA was maintained in 60-70% of patients at 5 years. Nonetheless, some patients require resumption of standard DMTs at some point after AHSCT, particularly with lower intensity non-myeloablative conditioning regimens. Similar to RRMS in a retrospective study from the Italian MS register 34.7%, patients with active SPMS who underwent AHSCT were more likely to experience a sustained disability improvement at 3 years after transplant vs 4.6% of patients treated by other DMTs (Boffa et al., 2023).

Previous estimates of overall transplant-related mortality in MS were >2%. The current estimate for AHSCT performed after 2012 is 0.2-0.3%. The improved safety is due to increased experience with the procedure, refinement of the protocol, and better selection of patients with lower risk of complications. The treatment regimen involves intense chemotherapy and has related side effects including hair loss, risk of infertility and infections. Typical hospital stay is about 4 weeks and there are several pre and post procedure scheduled visits for tests, and associated procedures.

'Stem cell treatment' is widely promoted on the internet and misused by unregulated centres. These centres offer the treatment to desperate unsuspecting patients, who often have far advanced MS or too mild a

Table 3
Unlicensed DMT with evidence of effectiveness

Unlicensed DMT in MS				
Drug	Indication	Best available evidence	Guidelines	Dose
Rituximab	Relapsing MS SPMS with disease activity	In the Hermes Trial rituximab group had reduced relapses at week 24 and 48 (20.3% vs. 40.0%, P=0.04) (Biogen). Cochrane review (Hauser et al., 2008) Retrospective observational study of 822 patients shows. benefit (Filippini et al., 2021)	Included in the WHO list of essential medicines for MS (World Health Organization 2023). Most common MS drug used in Sweden. Norwegian Institute of Public Health (NIPH) recommendation (Salzer et al., 2016, Stoltenberg & Atle, 2019) Highly cost effective (Stoltenberg & Atle, 2019) MENACTRIMS 2019 (Yamout et al., 2024)	500-1000 mg every 6 months
Azathioprine	Relapsing MS (AAN)	Cochrane review 2007 (Hagen et al., 2019) Effect on relapses : relative risk reduction (RRR) of 20 % at 2 years and 18 % at 3 years. Effect on progression: three small trials with a total of 87 patients: RRR = 42%; at three years	AAN MS guideline suggests that AZA is probably as effective as IFNB in preventing relapses (Class 2 study) .Clinicians may recommend azathioprine with relapsing forms of MS who do not have access to approved DMTs (Level C) (AAN 2018)	2-3mg /kg cumulative dose of 600g (Casetta et al., 2007)
Cyclophosphamide	Relapsing Aggressive MS Marburg MS Tumefactive MS	Numerous retrospective studies report benefit. Well controlled clinical trial data is limited. However, it remains a very effective option for aggressive. MS (La Mantia et al., 2007, Gladstone et al., 2006, Gómez-Figueroa et al., 2021) in the absence of other alternatives even for children (Fereidan-Esfahani & Tobin, 2021)	AAN (AAN 2018), MENACTRIMS (Yamout et al., 2024)	Cumulative dose 40g (Makhani et al., 2009) Adverse effects include gonadal toxicity, haemorrhagic cystitis, bladder cancer (0.7%), myelosuppression

disease. Considerable harm has been caused by such treatments (Julian et al., 2020). The patients most likely to benefit from AHSCT are young (approximately 50 years or less), with relatively recent disease onset (approximately 10 years or less), still ambulatory, with highly active MS as evidenced by recent clinical relapses or new MRI lesions, and continued disease activity despite treatment with high efficacy DMTs. Several organisations including the American Society for Blood and Marrow Transplantation (Cohen et al., 2019), European Bone marrow transplant working party (EBMT) (Sharrack et al., 2020) and US National MS Society have published policy statements that AHSCT is a reasonable option in such patients, who are at high risk for disability. It should only be performed in centres with established BMT programmes (Miller et al., 2021).

AHSCT is not considered a first line treatment in most MS patients. The committee, however, recognizes that there will be occasional instances where patients with treatment naïve active MS or active MS off treatment, will prefer only AHSCT for personal reasons. The decision to offer AHSCT in such situations is not to be taken lightly and should be done only after rigorous counselling of risks, benefits and alternative treatments. Strict institutional ethical approval and in accordance with international and national AHSCT guidelines must be followed. The details of these are outside the scope of this guideline.

Recommendation:

AHSCT is not considered a first line treatment in most MS patients. AHSCT is a treatment option for patients with highly active or rapidly evolving severe disease who are young (approximately 50 years or less), with relatively recent disease onset (approximately 10 years or less), still ambulatory and with continued disease activity despite ongoing treatment with at least one high efficacy DMT. It can also be considered for active SPMS with continued disease activity on high efficacy DMTs. It should only be performed in centres with established BMT programmes.

10. Discontinuing DMT

While MS is a chronic disease without cure, that does not mean that DMTs cannot be discontinued (McFaul et al., 2021). The use of ineffective therapy may pose harm to the individual, society, and the health system. With aging, inflammatory activity decreases while risk of DMTs increases. In the DISCOMS trial, patients that discontinued DMT were compared with those who did not with a primary outcome of development of new brain lesions or relapses. At an average follow-up time of about 2 years, approximately 5% of the group who continued medication vs 13% of the discontinuation group had new disease activity but statistically discontinuation was not inferior to continuation (ClinicalTrial.gov 2023).

Recommendations

- ***In patients with RRMS, older than 55 years of age and without evidence of disease activity for at least 5 years, discontinuing treatment may be considered.***
- ***In patients with progressive MS who are not ambulatory (EDSS 7) and without evidence of disease activity, a temporary break or pause in treatment may be considered. Patients and physicians are often understandably anxious about discontinuation. It is important to reassure them that treatment will be restarted if there is evidence of inflammatory activity (relapses or MRI lesions) or progression over and above that expected for the natural course of progressive MS.***
- ***A baseline scan at the time of discontinuing treatment followed by annual MRI scans and twice a year at least clinic visits are advised. Treatment must be restarted if unambiguous new relapse or MRI disease activity occurs.***

Patients should be counselled before discontinuation about

- pros and cons of stopping treatment including limited evidence of long-term safety of many drugs.
- the natural history of MS with decreasing relapses and inflammatory activity with age and duration of MS
- option of treating relapses with high-dose corticosteroids and plasma exchange and re-institution of DMT.
- emphasize that only the DMT is being discontinued and 'care' will continue.

11. Pediatric onset MS

Paediatric Onset MS (POMS) is defined as onset of MS before the age of 18. The criteria by the Pediatric International Study Group are most used for diagnosis in POMS (Krupp et al., 2013). The incidence is 0.87 per 100,000 individuals per year (Yan et al., 2020). Crude data in UAE indicate a prevalence amongst Emirati nationals for ages 10 to 14 years of 2.3/100 000 and 7.2/100 000 for ages 15 to 19 years (Ismail et al., 2018).

Treatment for acute attacks of MS follows the same principles as the adults with methyl prednisolone (20-30 mg/ kg/day up to a maximum of 1000 mg for five days) or plasma exchange, 5 exchanges each 1-1.5 times the plasma volume on alternate days (Cortese et al., 2011, Eyre et al., 2018).

11.1. DMT in Pediatric onset MS

All children with active MS are recommended to start DMT. There are 3 approved drugs for POMS: fingolimod (Chitnis et al., 2018) (EMA and FDA), teriflunomide (EMA) (Chitnis et al., 2021) and dimethyl fumarate (EMA) (European Medicines Agency 2022, Vermersch et al., 2022) (Table 3). However, there are considerable data on off label use of DMT used in adults with safety profile like that seen in adults.

11.2. Off Label DMT in pediatric Multiple Sclerosis

Almost all DMTS used in adults have been used in children off label (Makhani et al., 2009, Ismail et al., 2018, Kornbluh & Kahn, 2023, Brenton, 2022). These include interferons (Vermersch et al., 2022), glatiramer acetate, natalizumab, other S1P inhibitors, cyclophosphamide (Makhani et al., 2009) and CD20 agents (Krysko et al., 2020, Abdel-Mannan et al., 2021, Benallegue et al., 2024). Their efficacy over all mirrors adult MS and higher efficacy DMT prevent clinical and radiological disease activity and progression more than lower efficacy ones (Krysko et al., 2020, Abdel-Mannan et al., 2021, Benallegue et al., 2024). Several RCTS are ongoing.

Recommendations:

- ***All children with active MS are recommended treatment with dimethyl fumarate, fingolimod or teriflunomide.***
- ***Off label use of other high efficacy DMT can be justified in the presence of ongoing clinical or radiological disease activity on the above first line agents or as initial treatment for onset as highly active or RESMS following general principles used in adults.***

12. Pregnancy and DMT

Pregnancy is a state of relative immune tolerance, and the risk of disease activity is low. However, there is a postpartum increased risk of relapse. This however it is not universal and women who discontinue DMT, especially agents interfering with lymphocyte trafficking (S1P inhibitors and natalizumab), can have rebound disease during pregnancy itself (Bove & Houtchens, 2022, Dobson et al., 2019). DMT trials have excluded pregnant women or those planning pregnancy. So, data on the impact of DMT on both mother and child have emerged through registries documenting unplanned pregnancies and have taken years to accumulate useful information. Based on such registries, animal studies,

data from other diseases, there is now adequate data to classify DMT as safe, likely safe and unsafe in relation to pregnancy (Table 4). IFNB, Glatiramer, Natalizumab and dimethyl fumarate are safe (see below).

Fetal and neonatal B cell depletion is likely to impair immune function particularly with the huge array of pathogens a neonate is exposed to, and the many immunizations required in the first year of life. Accordingly, the labels of B cell depleting drugs recommend they be discontinued 6-12 months prior to conception (Iyer & Dobson, 2023, Dobson et al., 2023). However, increasing evidence suggests that this position is too conservative and a much shorter duration of discontinuation is sufficient based on several pieces of data. Transplacental transfer of maternal IgG antibodies reaches significant levels only by 22 weeks of gestation (Fouda et al., 2018). The serum concentrations of monoclonal antibodies after an infusion reach very low levels after 5 half-lives. Thus, both rituximab (median half-life of 3 weeks) and ocrelizumab (4 weeks) pose little risk of entering fetal circulation in clinically significant amounts at 22 weeks. So, conception 4 weeks after the last infusion gives an adequate safety margin. In practice, we recommend attempting conception after one menstrual cycle (defined as first day of a period up to the first day of next period) from the last dose. Table 5 summarises safety and timings of last dose before attempts at conception

Recommendation:

1. ***Glatiramer acetate and Beta interferons can be continued throughout pregnancy.***
2. ***Natalizumab can be continued until 34 weeks of pregnancy.***
3. ***Dimethyl fumarate can be continued until conception.***
4. ***Ofatumumab can be continued until conception.***
5. ***Pregnancy can be attempted after one menstrual cycle from the last dose of rituximab or ocrelizumab.***
6. ***Patients on teriflunomide should wait for serum levels to drop to < 0.02mg/dl which may take about 8 months to 2 years before attempting pregnancy. Alternatively, they should undergo the accelerated elimination procedure prior to pregnancy as per manufacturer guidelines*** (EMA 2023, Sanofi 2023).
7. ***Patients on dimethyl fumarate or teriflunomide can be switched to GA or IFNB during pregnancy.***
8. ***Patients on S1P modulators can be switched to natalizumab, or anti-CD20 agents.***
9. ***Monitoring B cell counts during pregnancy may help stratify risk of relapse if patients discontinued treatment with anti CD20 agents prior to pregnancy. Sustained low levels indicate low risk of relapse.***
10. ***Relapse during pregnancy can be treated with corticosteroids or plasma exchange.***

Table 5
MS DMT in pregnancy. Safety and timings of last dose before attempts at conception. *Menstrual cycle is defined as first day of menstruation to the first day of next menstruation.

MS DMT in pregnancy				
	Drug name	Last dose as per EMA/ FDA label in months	Last dose based on pharmacokinetic and pharmacodynamic data in months	Continuation in pregnancy
Safe (no wash out period needed before attempts to conceive)	Interferons	-	-	Yes
	Glatiramer acetate	-	-	Yes
	Corticosteroids	-	-	Yes
	Natalizumab	-	-	Yes. Last dose at or before 34 weeks
	Dimethyl fumarate (Yamout et al., 2024)	-	-	No
Likely safe (hile original labels suggest a washout period before attempts to conceive, several studies indicate safety).	Ofatumumab (Krysko et al., 2020)	6	Discontinue after pregnancy test positive	No
	Ocrelizumab	6-12	Can conceive after one menstrual cycle* from last dose	Consider re-treatment if no conception within 9–12 months of previous dose. Peripheral blood B cell counts (CD19 /CD20) counts can help determining dosing interval
	Rituximab	12	Can conceive after one menstrual cycle* from last dose	
Unsafe (wash out period needed before attempts to conceive)	Cladribine	6	6	No
	Ozanimod	3	3	No
	Fingolimod	2	2	No
	Ponesimod	7 days	7 days	No
	Siponimod	10 days	10 days	No
	Alemtuzumab	4	4	No

Table 4
DMT in Pediatric MS. ARR -absolute risk reduction

DMT in pediatric MS					
Drug	Approving Agency	Trial	Indication	Year approved	Results
Fingolimod	FDA EMA	Paradigms (Chitnis et al., 2018)	Age >10 years relapsing MS	2017	When compared with Avonex, 82% decrease in the ARR (absolute difference of 0.55; 95% CI 0.36–0.74) 0.53% decrease in annualized rate of new or newly enlarging T2 lesions (absolute difference of 0.47)
Teriflunomide	EMA	TERIKIDS (Chitnis et al., 2021)	age >10 years relapsing MS	2021	Primary end point (time to first confirmed clinical relapse) not met. Possibly because more patients than expected switched from the double-blind to the open-label treatment period because of high MRI activity; reduction in MRI activity, with a 55% reduction in new or newly enlarging T2 lesions and a 75% reduction in gadolinium enhancing lesions with significant treatment effect on a combined measure of MRI activity and clinical relapses
Dimethyl Fumarate	EMA MHRA	CONNECT (Vermersch et al., 2022)	>13 years RRMS	2022	Dimethyl fumarate Vs Interferon chance of relapse 34% vs 48%; number of new or enlarging T2 lesion 12.8% vs 2.8%;

13. Breast feeding and DMT

Breastfeeding should be supported in women with MS who wish to do so (Dobson et al., 2023, Capone et al., 2022, Gklinos & Dobson, 2023). If a patient chooses to breastfeed, the choice of restarting the DMT (if discontinued) depends on the likelihood of its transfer through breast milk (which in turn depends on molecular weight, protein binding, lipid solubility and transport mechanisms) and whether it will be absorbed from the new-born's gut and whether it is harmful to the new-born. The risk of relapse and the urgency to restart treatment is based on prior disease activity (Dobson et al., 2019, Iyer & Dobson, 2023). Table 6 classifies the DMT according to their safety profile in lactation. Monoclonal antibodies are too large to transfer into the breast milk an exception being the first week postpartum when gaps between breast acinar cells are large to transfer protective substances including immunoglobulins (colostrum) (Witzel, 2014). Monoclonal antibodies are destroyed in the mature infant's gut and have limited absorption (Witzel, 2014). The panel is of the opinion monoclonal antibody DMT can be safely recommenced in the 2nd week post-partum at the last used dose pre pregnancy in most patients. Breast feeding should be avoided for 4 hours after an infusion or injection.

Recommendations:

- ***Women with MS may breast feed due to its many benefits to mother and child.***
- ***Choose a DMT that has limited impact on neonate even if absorbed.***
- ***Continue breastfeeding with early resumption of a DMT unlikely to be present in significant amounts in the breast milk. These include monoclonal antibodies, interferons and glatiramer acetate.***

Table 6
MS DMT during breast feeding.

MS DMT during breast feeding		
Safe	Interferons, Glatiramer	
	Corticosteroids. Breastfeeding should not be undertaken within four hours of infusion	
	Natalizumab. Avoid in the first 7 days of breastfeeding and for 4 hours after infusion	
Likely safe	Ofatumumab	While original labels are cautious, the biological properties (mol. Weight ~150 KD) of the Mab and reported safety so far support use. Very little secretion in breast milk and very limited absorption from infant gut. Avoid in the first 7 days of lactation and 4 hours after each infusion or injection
	Ocrelizumab	
	Rituximab	
	Alemtuzumab	Avoid treatment during first 7 days of lactation Avoid lactation on infusion days
	Cladribine	Only detectable in breastmilk for a short time Suspend breastfeeding till 7 days after last dose
Unsafe	Teriflunomide, Mitoxantrone, S1P inhibitors, Dimethyl fumarate	

14. Conclusions

MS is a complex chronic disease with high risk of long-term disability. In this broad and yet specific DMT guideline we have tried to put together pragmatic amalgamation of best practice from across the world that takes into account UAE's unique situation and demography. The overall goal of the treatment guideline is to facilitate the most appropriate DMT to the widest number of patients and to facilitate emerging treatments earlier. Where data is unavailable or controversial, a common sense approach has been adopted rather than leave physicians and patients in limbo. It is expected that these guidelines will be updated periodically as new data becomes available.

Funding

This guideline was not funded, but the meetings were organised and facilitated by the non-profit organisation- National Multiple Sclerosis Society of United Arab Emirates.

CRediT authorship contribution statement

Anu Jacob: Writing – review & editing, Writing – original draft. **Ahmed Osman Shatila:** Writing – review & editing. **Jihad Inshasi:** Writing – review & editing. **Joelle Massouh:** Writing – review & editing. **Ruquia Mir:** Writing – review & editing. **Suzan Noori:** Writing – review & editing. **Bassem Yamout:** Writing – review & editing.

Declaration of competing interest

Anu Jacob has received advisory board fees and speakers fee from Astra Zeneca.

Ahmed Shatila has received speaker's honoraria, advisory board fees, travel grants from Novartis, Sanofi Genzyme, Roche, Merck, Jansen, Biologix, pfizer, Boehringer Ingelheim, AstraZeneca, Lundbeck and Argenx, Bayer, Biogen and received research grants from Novartis, AstraZeneca and Argenx.

Jihad Inshasi has received speaker's honoraria from Bayer, Biogen, Biologix, Merck, Novartis, Roche, Sanofi; Research grants from Merck, Novartis; Advisory board fees from Bayer, Biogen,Merck, Novartis, Roche, Sanofi

Joelle Massouh has received speakers' honoraria, travel, grants and advisory board fees from AstraZeneca, Biogen, Biologix, Janssen, Merck, Novartis, Roche, and Sanofi.

Ruquia Mir has received speaker's honoraria, advisory board fees and travel grants from Merck Sanofi Novartis Roche

Suzan Noori has no disclosures.

Bassem Yamout has received speaker's honoraria travel, grants and advisory board fees from Bayer, Biogen, Biologix, Genpharm, Merck, Novartis, Roche, Sanofi, Genzyme and research grants from Bayer, Biogen, Biologix, Merck, Novartis, Pfizer

Acknowledgements

The authors acknowledge the support of the UAE National MS society in particular Dr Fatima Al Kaabi, Ghalya Ali, Maral Alexanderian, Yasmin Mitwally, and Meera Al Mutawa (Sheikha Salama Bint Hamdan Al Nahyan Foundation) in facilitating this guideline. The authors also acknowledge the critical review and comments by UAE neurologists: Drs Abubaker Almadani, Ali Hassan, Areen Said, Beatrice Benedetti, Deeb Kayed, Halprashant Sathyanarayana, Miklos Szolics, Mona Thakre, Mustafa Shakra, Devdutt Nayak Kotekar, Naji Riachi, Pournami Sarath Chandran and Reem Al Suwaidi

References

AAN *Summary of practice guideline for clinicians practice guideline: disease-modifying therapies for adults with multiple sclerosis starting disease-modifying therapy (DMT) Recommendations*.

Abdel-Mannan, O.A., et al., 2021. Use of disease-modifying therapies in pediatric relapsing-remitting multiple sclerosis in the United Kingdom. Neurol. Neuroimmunol. Neuroinflamm. 8.

Barnes, D., et al., 1997. Randomised trial of oral and intravenous methylprednisolone in acute relapses of multiple sclerosis. Lancet 349, 902–906.

Bazi, A., Baghbanian, S.M., Ghazaeian, M., Saeedi, M., Hendoiee, N., 2021. Efficacy and safety of oral prednisolone tapering following intravenous methyl prednisolone in patients with multiple sclerosis relapses: a randomized, double-blind, placebo-controlled trial. Mult. Scler. Relat. Disord. 47.

Benallegue, N., et al., 2024. Highly effective therapies as first-line treatment for pediatric-onset multiple sclerosis. JAMa Neurol. 81, 273.

Beutler, E., et al., 1996. The treatment of chronic progressive multiple sclerosis with cladribine. Proc. Natl. Acad. Sci. USA 93, 1716–1720.

Biogen. Tysabri safety consideration. https://www.tysabri.com/en_us/home/about/safety-considerations.html?accKey=3.

Boffa, G., et al., 2023. Hematopoietic stem cell transplantation in people with active secondary progressive multiple sclerosis. Neurology 100, E1109–E1122.

Bove, R. M. & Houtchens, M. K. *Pregnancy management in multiple sclerosis and other demyelinating diseases*. (2022).

Brenton, J.N., 2022. Pediatric acquired demyelinating disorders. Continuum (Minneap. Minn) 28, 1104–1130.

Burt, R.K., et al., 2020. Health economics and patient outcomes of hematopoietic stem cell transplantation versus disease-modifying therapies for relapsing remitting multiple sclerosis in the United States of America. Mult. Scler. Relat. Disord. 45, 102404.
Burton, J.M., O'Connor, P.W., Hohol, M., Beyene, J, 2009. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD006921.PUB2.
Capone, F., et al., 2022. Disease-modifying drugs and breastfeeding in multiple sclerosis: a narrative literature review. Front. Neurol. 13 https://doi.org/10.3389/fneur.2022.851413. Preprint at.
Casetta, I., Iuliano, G., Filippini, G., 2007. Azathioprine for multiple sclerosis. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD003982.pub2. Preprint at.
Chitnis, T., Giovannoni, G., Trojano, M., 2018. Complexity of MS management in the current treatment era. Neurology. 90, 761–762. https://doi.org/10.1212/WNL.0000000000005399. Preprint at.
Chitnis, T., et al., 2018. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. New Engl. J. Med. 379, 1017–1027.
Chitnis, T., et al., 2021. Safety and efficacy of teriflunomide in paediatric multiple sclerosis (TERIKIDS): a multicentre, double-blind, phase 3, randomised, placebo-controlled trial. Lancet Neurol. 20, 1001–1011.
Citterio, A., et al., 2000. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Cochrane Database Syst. Rev. 2000.
Claflin, S.B., Broadley, S., Taylor, B.V., 2019. The effect of disease modifying therapies on disability progression in multiple sclerosis: a systematic overview of meta-analyses. Front. Neurol. 10 https://doi.org/10.3389/fneur.2018.01150. Preprint at.
ClinicalTrial.gov. DISCOMS Trial. https://clinicaltrials.gov/ct2/show/study/NCT03073603 (2023).
Cohen, J.A., et al., 2019. Autologous hematopoietic cell transplantation for treatment-refractory relapsing multiple sclerosis: position statement from the american society for blood and marrow transplantation. Biol. Blood Marrow TransPlant 25, 845–854.
Cortese, I., et al., 2011. Evidence-based guideline update: Plasmapheresis in neurologic disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 76, 294–300.
Cree, B.A.C., et al., 2019. Silent progression in disease activity–free relapsing multiple sclerosis. Ann. Neurol. 85, 653–666.
Cree, B.A.C., et al., 2021. Secondary progressive multiple sclerosis: new insights. Neurology. 97, 378–388.
Cross, A. & Riley, C. *Treatment of multiple sclerosis*. (2022).
De Stefano, N., et al., 2018. Radiologically isolated syndrome or subclinical multiple sclerosis: MAGNIMS consensus recommendations. Mult. Scler. 24, 214–221.
Dobson, R., et al., 2019. UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines. Pract. Neurol. 19, 106–114. https://doi.org/10.1136/practneurol-2018-002060. Preprint at.
Dobson, R., et al., 2023. Anti-CD20 therapies in pregnancy and breast feeding: a review and ABN guidelines. Pract. Neurol. 23, 6–14.
Eckert, S. P., Weinstock-Guttman, B. & Kreiger, S. Point/counterpoint: food and drug administration multiple sclerosis categorization changes. https://practicalneurology.com/articles/2020-feb/pointcounterpoint-food-and-drug-administration-multiple-sclerosis-categorization-changes (2020).
ECTRIMS & EAN. ECTRIMS/EAN Clinical Guidelines on MS treatment: an update. https://conferences.medicom-publishers.com/specialisation/neurology/ectrims-2021/ectrims-ean-clinical-guidelines-on-ms-treatment-an-update/ (2021).
EMA. Aubagio Teriflunamide. *Summary of product charecteristics* (2023).
European Medicines Agency. Dimethyl fumarate authorisation . https://www.ema.europa.eu/en/medicines/human/EPAR/tecfidera (2022).
Eyre, M., Hacohen, Y., Barton, C., Hemingway, C., Lim, M., 2018. Therapeutic plasma exchange in paediatric neurology: a critical review and proposed treatment algorithm. Dev. Med. Child Neurol. 60, 765–779.
Farez, M.F., et al., 2019. Practice guideline update summary: Vaccine-preventable infections and immunization in multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 93, 584–594.
Fassas, A., et al., 1997. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. Bone Marrow TransPlant 20, 631–638.
FDA. FDA approves new oral treatment for multiple sclerosis. https://www.fda.gov/news-events/press-announcements/fda-approves-new-oral-treatment-multiple-sclerosis (2019).
Fereidan-Esfahani, M., Tobin, W.O., 2021. Cyclophosphamide in treatment of tumefactive multiple sclerosis. Mult. Scler. Relat. Disord. 47.
Filippini, G., Kruja, J., Del Giovane, C., 2021. Rituximab for people with multiple sclerosis. Cochrane Database Syst. Rev. 11, CD013874 https://doi.org/10.1002/14651858.CD013874.pub2. Preprint at.
Fisniku, L.K., et al., 2008. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain 131, 808–817.
Fouda, G.G., Martinez, D.R., Swamy, G.K., Permar, S.R., 2018. The impact of IgG transplacental transfer on early life immunity. Immunohorizons 2, 14–25.
Gómez-Figueroa, E., et al., 2021. Cyclophosphamide treatment in active multiple sclerosis. Neurological Sciences 42, 3775–3780.
GDP per capita (current US$) - United Kingdom, United States, European Union, United Arab Emirates | Data. https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=GB-US-EU-AE&most_recent_value_desc=true.
Gklinos, P., Dobson, R., 2023. Monoclonal antibodies in pregnancy and breastfeeding in patients with multiple sclerosis: a review and an updated clinical guide. Pharmaceuticals 16. https://doi.org/10.3390/ph16050770. Preprint at.
Gladstone, D.E., et al., 2006. High-dose cyclophosphamide for moderate to severe refractory multiple sclerosis. Arch. Neurol. 63, 1388–1393.
Gout, O., et al., 2011. Prior suggestive symptoms in one-third of patients consulting for a 'first' demyelinating event. J. Neurol. Neurosurg. Psychiatry 82, 323–325.
Gunhild Hagen, Ulrikke Lund, Atle Fretheim & Vida Hamidi. *Disease modifying treatments for relapsing remitting multiple sclerosis. a health economic evaluation*. https://www.fhi.no/en/publ/2019/Disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis/ (2019).
Hartung, H.P., et al., 2002. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet 360, 2018–2025.
Hauser, S. L. et al. *B-Cell Depletion with Rituximab in Relapsing-Remitting Multiple Sclerosis*. www.nejm.org (2008).
Hawker, K., et al., 2009. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann. Neurol. 66, 460–471.
Hollen, C.W., Paz Soldán, M.M., Rinker, J.R., Spain, R.I., 2020. The future of progressive multiple sclerosis therapies. Fed. Pract. 37, S43–S49.
Inshasi, J., Thakre, M., 2011. Prevalence of multiple sclerosis in Dubai, United Arab Emirates. Int. J. Neurosci. 121, 393–398.
Ismail, F.Y., et al., 2018. Pediatric multiple sclerosis in the United Arab Emirates: characteristics from a multicenter study and global comparison. J. Child Neurol. 33, 422–427.
Iyer, P., Dobson, R., 2023. Multiple sclerosis in pregnancy: a commentary on disease modification and symptomatic drug therapies. Neurol. Ther. 12, 1–10.
Julian, K., Yuhasz, N., Rai, W., Salerno, J.A., Imitola, J., 2020. Complications from 'stem cell tourism' in neurology. Ann. Neurol. 88, 661–668.
Kappos, L., et al., 2018. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 391, 1263–1273.
Kappos, L., et al., 2020. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. JAMa Neurol. 77, 1132–1140.
Kornbluh, A.B., Kahn, I., 2023. Pediatric multiple sclerosis. Semin. Pediatr. Neurol. 46.
Krupp, L.B., et al., 2013. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: Revisions to the 2007 definitions. Multiple Sclerosis J. 19, 1261–1267. https://doi.org/10.1177/1352458513484547. Preprint at.
Krysko, K.M., et al., 2020. Real-world effectiveness of initial disease-modifying therapies in pediatric multiple sclerosis. Ann. Neurol. 88, 42–55.
La Mantia, L., Milanese, C., Mascoli, N., D'Amico, R., Weinstock-Guttman, B, 2007. Cyclophosphamide for multiple sclerosis. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD002819.pub2.
Laurson-Doube, J., et al., 2021. Ethical use of off-label disease-modifying therapies for multiple sclerosis. Mult. Scler. J. 27, 1403–1410.
Lebrun-Frénay, C., et al., 2023. The radiologically isolated syndrome: revised diagnostic criteria. Brain. https://doi.org/10.1093/brain/awad073 awad073.
Lebrun-Frénay, C., et al., 2023. Teriflunomide and time to clinical multiple sclerosis in patients with radiologically isolated syndrome: the TERIS randomized clinical trial. JAMa Neurol. https://doi.org/10.1001/jamaneurol.2023.2815.
Lebrun-Frenay, C., et al., 2020. Radiologically isolated syndrome: 10-year risk estimate of a clinical event. Ann. Neurol. 88, 407–417.
Liu, S., Liu, X., Chen, S., Xiao, Y., Zhuang, W., 2017. Oral versus intravenous methylprednisolone for the treatment of multiple sclerosis relapses: a meta-analysis of randomized controlled trials. PLoS. One 12.
Lublin, F.D., et al., 2014. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83, 278–286.
Maarouf, A., et al., 2024. Active and non-active progression independent of relapse activity within the first 20 years of relapsing multiple sclerosis. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2024-333597 jnnp-2024-333597.
Makhani, N., et al., 2009. Cyclophosphamide therapy in pediatric multiple sclerosis. Neurology 72, 2076–2082.
McFaul, D., Hakopian, N.N., Smith, J.B., Nielsen, A.S., Langer-Gould, A., 2021. Defining benign/burnt-out MS and discontinuing disease-modifying therapies. Neurol. Neuroimmunol. Neuroinflamm. 8.
Miller, A.E., et al., 2021. Autologous hematopoietic stem cell transplant in multiple sclerosis: recommendations of the national multiple sclerosis society. JAMa Neurol. 78, 241–246.
Mohammed, E.M.A., 2016. Multiple sclerosis is prominent in the Gulf states: review. Pathogenesis 3, 19–38. https://doi.org/10.1016/j.pathog.2016.04.001. Preprint at.
Montalban, X., et al., 2017. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N. Engl. J. Med. 376, 209–220.
Montalban, X., et al., 2018. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Eur. J. Neurol. 25, 215–237.
Morrow, S. A. Stoian, C. A, Dmitrovic, J, Chan, S C & Metz, L. M. *Brief communications the bioavailability of IV methylprednisolone and oral prednisone in multiple sclerosis*. http://mscare.com. (2004).
Muraro, P.A., et al., 2017. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. Nat. Rev. Neurol. 13, 391–405.
National MS Society USA. Disease-modifying therapies for MS. *Treating MS* https://www.nationalmssociety.org/Treating-MS/Medications (2023).
NHS England. Flow chart NHS England MS disease modifying treatment algorithm. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-FlowChartMultiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf (2019).

NHS England. *Treatment algorithm for multiple sclerosis disease-modifying therapies NHS England Reference: 170079ALG treatment algorithm for multiple sclerosis disease-modifying therapies contents*. (2019).
NICE Technology appraisal guidance [TA616]. Cladribine for treating relapsing–remitting multiple sclerosis. https://www.nice.org.uk/guidance/ta616/chapter/1-Recommendations (2019).
Okuda, D.T., et al., 2009. Incidental MRI anomalies suggestive of multiple sclerosis. Neurology 72, 800–805.
Okuda, D.T., et al., 2023. Dimethyl fumarate delays multiple sclerosis in radiologically isolated syndrome. Ann. Neurol. 93, 604–614.
Ontaneda, D., Chitnis, T., Rammohan, K., Obeidat, A.Z., 2023. Identification and management of subclinical disease activity in early multiple sclerosis: a review. J. Neurol. https://doi.org/10.1007/s00415-023-12021-5. Preprint at.
Otero-Romero, S., et al., 2023. ECTRIMS/EAN consensus on vaccination in people with multiple sclerosis: Improving immunization strategies in the era of highly active immunotherapeutic drugs. Multiple Sclerosis J. https://doi.org/10.1177/13524585231168043. Preprint at.
Perumal, J.S., et al., 2008. Oral prednisone taper following intravenous steroids fails to improve disability or recovery from relapses in multiple sclerosis. Eur. J. Neurol. 15, 677–680.
Rae-Grant, A, et al., 2018. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Neurology 90, 777–788. https://doi.org/10.1212/WNL.0000000000005347. Preprint at.
Ramo-Tello, C., et al., 2014. A randomized clinical trial of oral versus intravenous methylprednisolone for relapse of MS. Mult. Scler. 20, 717–725.
Rice, G.P.A., Filippi, M., Comi, G., 2000. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Neurology. 54, 1145–1155.
Salzer, J. et al. *Rituximab in multiple sclerosis a retrospective observational study on safety and efficacy*. (2016).
Sanofi. Accelerated elimination procedure for Teriflunamide. https://www.aubagiohcp.com/prescribing-aubagio (2023).
Schiess, N., et al., 2016. How global MS prevalence is changing: a retrospective chart review in the United Arab Emirates. Mult. Scler. Relat. Disord. 9, 73–79.
Sharrack, B., et al., 2020. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). Bone Marrow TransPlant 55, 283–306.
Sharrad, D., Chugh, P., Slee, M., Bacchi, S., 2023. Defining progression independent of relapse activity (PIRA) in adult patients with relapsing multiple sclerosis: A systematic review☆. Mult. Scler. Relat. Disord. 78 https://doi.org/10.1016/j.msard.2023.104899. Preprint at.
Simonsen, C.S., et al., 2021. Early high efficacy treatment in multiple sclerosis is the best predictor of future disease activity over 1 and 2 years in a norwegian population-based registry. Front. Neurol. 12.
Sormani, M.P., Muraro, P.A., Saccardi, R., Mancardi, G., 2017. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. Mult. Scler. 23, 201–204.
Sormani, M. P. et al. *Autologous hematopoietic stem cell transplantation in multiple sclerosis a meta-analysis*. (2017).
Stoltenberg, C. & Atle, F. *Title disease-modifying treatments for relapsing remitting multiple sclero*. (2019).
Vermersch, P., et al., 2022. Effect of dimethyl fumarate vs interferon β-1a in patients with pediatric-onset multiple sclerosis: the CONNECT randomized clinical trial. JAMa Netw. Open. 5, e2230439. –e2230439.
Visser, L.H., et al., 2004. A randomized, double-blind, placebo-controlled pilot study of i.v. immune globulins in combination with i.v. methylprednisolone in the treatment of relapses in patients with MS. Mult. Scler. 10, 89–91.
Wattjes, M.P., et al., 2021. 2021 MAGNIMS–CMSC–NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. Lancet Neurol. 20, 653–670.
Weiner, H.L., et al., 1989. Double-blind study of true vs. sham plasma exchange in patients treated with immunosuppression for acute attacks of multiple sclerosis. Neurology 39, 1143–1149.
Weinshenker, B.G., 2001. Plasma exchange for severe attacks of inflammatory demyelinating diseases of the central nervous system. J. Clin. Apher. 16, 39–42.
Wiendl, H., et al., 2021. Multiple Sclerosis Therapy Consensus Group (MSTCG): position statement on disease-modifying therapies for multiple sclerosis (white paper). Ther. Adv. Neurol. Disord. https://doi.org/10.1177/17562864211039648 vol. 14 Preprint at.
Witzel, S.J., 2014. Lactation and the use of biologic immunosuppressive medications. Breastfeeding Med. 9, 543–546.
World Health Organization. WHO model list of essential medicines - 23rd list, 2023. 6–6 https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02 (2023).
Yamout, B.I., et al., 2018. Safety and efficacy of rituximab in multiple sclerosis: a retrospective observational study. J. Immunol. Res. 2018.
Yamout, B., et al., 2020. Consensus recommendations for the diagnosis and treatment of multiple sclerosis: 2019 revisions to the MENACTRIMS guidelines. Mult. Scler. Relat. Disord. 37 https://doi.org/10.1016/j.msard.2019.101459. Preprint at.
Yamout, B., et al., 2024. Consensus recommendations for diagnosis and treatment of Multiple Sclerosis: 2023 revision of the MENACTRIMS guidelines. Mult. Scler. Relat. Disord. 83, 105435.
Yan, K., Balijepalli, C., Desai, K., L, G.-M.S., 2020. Epidemiology of pediatric multiple sclerosis: a systematic literature review and meta-analysis. undefined. Elsevier.
Zeineddine, M.M., Yamout, B.I., 2020. Treatment of multiple sclerosis in special populations: the case of refugees. Mult. Scler. J. Exp. Transl. Clin. 6.