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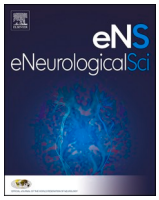

Update in multiple sclerosis

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ABSTRACT

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 evidence pointing towards a multifactorial etiology involving both environmental and genetic factors. The prevalence and incidence rates of MS have been steadily increasing worldwide over the last few decades. The diagnosis of MS relies on incorporating clinical and paraclinical findings to prove dissemination in space and time. Appropriate selection of MS therapies is critical to maximize patient benefit. 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. This review will cover the epidemiology of MS, new concepts in immunopathogenesis and etiology, recent diagnostic criteria and red flags for avoiding misdiagnosis, therapeutic advances, disease management during pregnancy, and updated treatment guidelines.

Multiple Sclerosis (MS) is a chronic demyelinating disorder of the central nervous system (CNS) that affects predominantly patients aged 20–40 years. The epidemiology of MS is changing worldwide, as is the understanding of its immunopathogenesis and natural history, with new evidence pointing towards a multifactorial etiology involving both environmental and genetic factors. A groundbreaking study found that EBV infection increased the risk of developing MS by 32 folds and that virtually all patients with MS were previously infected with the virus, suggesting that EBV is the leading cause of MS [1]. The prevalence and incidence rates of MS have been steadily increasing worldwide over the last few decades with the highest rates reported from Northern Europe and North America [2].

The diagnosis of MS relies on incorporating clinical and paraclinical findings to prove dissemination in space and time (DIS and DIT) and exclude alternative diseases that can explain the findings at hand. Based on the 2017 McDonald criteria, the diagnosis of MS can be made in a patient presenting with symptoms consistent with a CNS inflammatory demyelinating event and evidence of DIS as demonstrated by one or more T2-hyperintense lesions on MRI in two or more of four areas of the CNS: periventricular, cortical or juxtacortical, infratentorial and spinal cord, and DIT as demonstrated by the simultaneous presence of enhancing and non-enhancing lesions or by a new T2-hyperintense lesion on follow-up MRI irrespective of the timing of the MRI or by the presence of oligoclonal bands (OCB) in the cerebrospinal fluid. Despite the high sensitivity and specificity of these criteria, misdiagnosis was still an issue with around 15 % of patients initially diagnosed with MS turning out to have a different disease. The recent proposal for the 2024 updated Mc Donald criteria added the optic nerve as a 5th topography and 2 MRI biomarkers, the central vein sign (CVS) and paramagnetic rim lesions, to increase the sensitivity and specificity of the diagnosis of MS [3].

Recent research has shown that progression independent of relapses or PIRA is present in the early stages of the disease and in fact is the major cause of disability in relapsing remitting MS (RRMS) [4]. In addition, early uncontrolled inflammatory disease activity leading to axonal loss can exhaust brain reserve and neuroplasticity capacity and shorten time to disability progression.

Current treatment guidelines stress the importance of early and complete suppression of inflammatory activity in RRMS, as reflected by relapses and new/enhancing lesions on MRI.

Studies have shown that early treatment, especially with high efficacy therapies such as the monoclonal antibodies and cladribine can significantly improve long-term outcomes, including reducing the risk of progression to secondary progressive MS [5,6].

Several key factors have been associated with an increased risk of future disability progression: older age at onset, male sex, relapse frequency and severity, incomplete recovery from early relapses, high lesion load on MRI and presence of spinal cord or infratentorial lesions. The presence of these poor prognostic factors at disease onset should prompt the use of high efficacy therapies early on. There are more than

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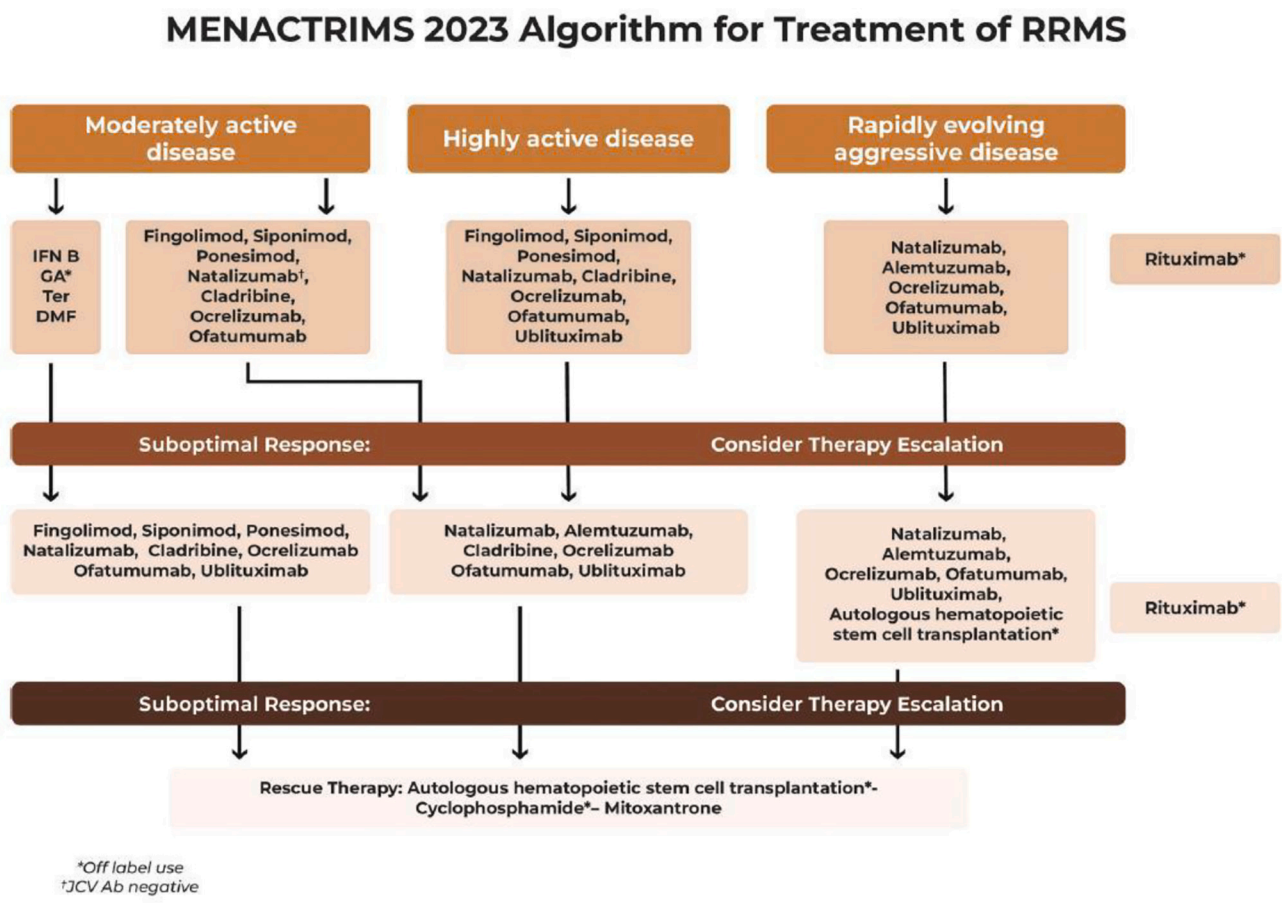

Fig. 1. Treatment guidelines for relapsing remitting multiple sclerosis.

20 approved therapies for the treatment of MS ranging from moderate efficacy drugs such as interferons, glatiramer acetate, teriflunomide and dimethyl fumarate, to intermediate efficacy therapies such as fingolimod, siponimod, ponesimod and ozanimod to high efficacy therapies such as natalizumab, ocrelizumab, ofatumumab, ublituximab, alemtuzumab and cladribine. Treatment selection based on the presence or absence of poor prognostic factors is crucial in preventing relapses and disability progression. This is reflected in most current treatment algorithms including our recently published MENACTRIMS (Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis) Guidelines for treatment of RRMS (Fig. 1) [7].

Autologous hematopoietic stem cell transplantation (AHSCT) is an emerging treatment for MS, especially in patients with early aggressive disease unresponsive to conventional therapies. Recent less aggressive immunosuppressive regimens have significantly decreased mortality and morbidity rates without affecting efficacy of AHSCT. Treated patients achieved long term control of their disease with rates of NEDA (no evidence of disease activity), i.e. no relapses, new MRI lesions or disability progression, approaching 60–70 % at 5 years follow-up. Recent guidelines for the use of AHSCT in patients with MS were published by the European Society for Blood and Marrow Transplantation (EBMT) [8].

The radiologically isolated syndrome (RIS) refers to patients with MRI lesions typical of MS but without any associated neurological symptoms that could be attributed to MS. In the recently proposed 2024 McDonald criteria, RIS was considered as an early stage of MS if it fulfills criteria for DIS in addition to DIT, positive OCB, or presence of lesions with CVS. More than 50 % of patients with RIS will develop symptoms suggestive of MS over the next 10 years. Younger age, oligoclonal bands, spinal cord, infratentorial and enhancing lesions were the major risk factors for clinical conversion [9]. Two recent clinical trials confirmed the efficacy of 2 therapies, teriflunomide and dimethyl fumarate, in reducing the risk of conversion to clinical MS in patients with RIS [9].

Our approach to pregnancy and breastfeeding in women with MS has changed drastically over the last few years. IgG antibodies do not cross the placenta in any significant amount before week 20 of pregnancy. Accordingly, anti-CD20 monoclonal antibodies with half-lives ranging from 16 to 26 days are usually cleared from the mother's serum before week 20 of pregnancy if conception occurs after the last administered dose. Natalizumab has been shown to be safe during pregnancy until week 30–34. Due to its short half-life and so far reassuring data from the international pregnancy registry, dimethyl fumarate is the only oral therapy that can be maintained until conception. Based on this recent scientific evidence more women are currently attempting conception while on treatment. Breastfeeding is beneficial for both mother and infant. The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months and continued breastfeeding up to 2 years of age. Although oral therapies are contraindicated in breastfeeding MS patients, high molecular weight drugs such as interferons, glatiramer acetate or monoclonal antibodies can be safely administered due to very low RID (Relative Infant Dose) [10].

CRediT authorship contribution statement

Bassem Yamout: Writing – original draft.

Declaration of competing interest

None.

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