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Review article

Consensus recommendations for the diagnosis and treatment of multiple sclerosis: 2019 revisions to the MENACTRIMS guidelines

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A B S T R A C T

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

1. Background

Multiple Sclerosis (MS) is a chronic demyelinating disorder of the central nervous system (CNS) that affects predominately patients aged 20–40 years. The epidemiology of MS is changing worldwide, as is the understanding of its immunopathogenesis and natural history, with new evidence pointing towards a multifactorial etiology involving both environmental and genetic factors (Goodin, 2014; Trojano et al., 2011). The prevalence and incidence rates of MS have been steadily increasing worldwide over the last few decades including the Middle East North Africa (MENA) region (El-Salem et al., 2006; Al-Hashel et al., 2008; Inshasi and Thakre, 2011; Deleu et al., 2013; Alroughani et al., 2014; Etemadifar et al., 2014). The field of MS therapeutics is evolving rapidly as several novel disease modifying therapies (DMTs) have been added to our armamentarium in the last decade. There is a clear need to unify and update the diagnostic and therapeutic paradigms across the MENA region as most countries in the region are in the process of establishing specialized MS centers. On the other hand, some diagnostic mimickers of MS, such as neurobrucellosis, neuro-Behçet, Toxocara canis myelitis (Jabbour et al., 2011), HTLV-1 myelitis, and others might be unique or much more common in the Middle East compared to Europe or North America, which necessitates a slightly different diagnostic approach. Neurologists from different countries in the MENA region with experience in the management of MS, met at a workshop

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sponsored by the Middle East North Africa Committee for Treatment And Research in Multiple Sclerosis (MENACTRIMS), to update previously published consensus guidelines for the diagnosis and treatment of MS (Yamout et al., 2013). The members represent countries in the region with specialized MS clinics/centers or dedicated neurological services to MS patients. The panel consists of academic, hospital-based and community general neurologists with expertise in MS, along with specialized MS neurologists in order to ensure a wide diversity of opinions.

1.1. Diagnosis of multiple sclerosis

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

Historically, the diagnosis was based solely on clinical evidence of dissemination in time and space as proposed by Schumacker et al. (1965). Poser et al. in 1983 introduced the concepts of clinical attack, a symptom of neurological dysfunction lasting more than 24 h, and paraclinical evidence demonstrating by any test, the existence of non-clinical lesions in the CNS such as neurophysiologic tests (evoked potentials) and OCB in CSF. The Poser criteria were developed before the widespread use of MRI which subsequently resulted in its increasing adoption as paraclinical evidence in the diagnosis of MS (Poser et al., 1983). With the development of effective DMTs, it became essential to identify patients with clinically isolated syndrome (CIS) at high risk of developing MS. The diagnostic criteria proposed by McDonald in 2001, and revised three times so far in 2005, 2010 and 2017 expanded the role of MRI in proving dissemination in space (DIS) and time (DIT), and allowed for earlier diagnosis of MS (McDonald et al., 2001; Polman et al., 2011; Thompson et al., 2018).

With respect to MRI protocol, it is recommended to adopt the 2015 MAGNIMS guidelines on the use of MRI in multiple sclerosis (Rovira et al., 2015).

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

DIT can be fulfilled by the presence of a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, or the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any point in time. Again, unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required. If criteria for DIS are fulfilled, the presence of CSF-specific oligoclonal bands allows a diagnosis of multiple sclerosis in the absence of DIT.

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

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

Table 1
Red flags in the diagnosis of multiple sclerosis.

Clinical presentations:
- No dissemination in time/space
- Onset <10 or >55 years of age
- Prominent fever/headache, impairment of consciousness,
- Abrupt hearing loss
- Non-scotomatous field defect
- Cortical features (seizures, aphasia, cortical blindness)
- Encephalopathy

Optic Neuritis:
- Bilateral presentation
- Severe pain that restricts movement or awakens patient
- Very severe visual loss without recovery after 1 month
- Uveitis
- Retinal exudates or hemorrhages, severe optic disc edema and vitreous reaction
- History of cancer

Transverse Myelitis
- Hyperacute non progressive onset
- Complete involvement of the spinal segment
- Progressive myelopathy in the absence of bladder involvement
- Anterior spinal artery distribution
- Radicular pain
- Cauda Equina Syndrome
- Co-existing lower motor neuron (LMN) signs

Brainstem/Cerebellar• Hyperacute onset in a vascular territory• Fluctuating or fatigable ocular or bulbar symptoms
Complete external ophthalmoplegia

MRI:
- Brain: Normal, small lesions <3 mm, prominent gray matter involvement, hydrocephalus, absence of callosal or periventricular lesions, symmetric confluent WM lesions, meningeal enhancement, or simultaneous enhancement of all lesions.
- Spine: Extensive lesion spanning 3 or more segments, swelling, full thickness lesions, leptomenengial enhancement, T1 hypointense lesions

CSF:
- Normal,
- Absence of OCB (By isoelectric focusing technique)
- White blood cell count > 50,
- Protein > 80 mg/dl

All revised criteria are still based on excluding other possible entities that could explain the patient's clinical and radiological findings. Patients who have atypical clinical or MRI findings should be thoroughly investigated to identify MS mimickers. Atypical clinical presentations such as bilateral optic neuritis, hyperacute myelitis with predominately motor involvement, seizures, extrapyramidal symptoms or confusion may necessitate further appropriate workup. Atypical MRI findings such as simultaneous enhancement of all lesions, persistent enhancement of the lesions for more than 6 months, lack of periventricular lesions, or a longitudinally extensive lesion in the spinal cord require more attention to exclude other diagnoses (Miller et al., 2008). A list of the most common red flags is outlined in Table 1. Although CSF analysis is not required to establish the diagnosis of MS, it is recommended to obtain CSF in atypical presentations in order to exclude other diseases, especially in pediatric patients. The potential list of MS mimickers is exhaustive, with a variety of available tests to exclude different possibilities (Table 2). Considering such diagnostic alternatives randomly has a very low yield and leads to unnecessary workup. The differential and subsequent workup should be guided by 'atypical' clinical/paraclinical findings or red flags that are specific to each case.

A revised MS phenotype classification has been recently published to improve consistency in defining patient groups (Table 3) (Lublin et al., 2014). CIS is now recognized as the initial manifestation of the disease and both CIS and relapsing phenotypes are classified as either active or inactive. Disease activity is defined by either clinical relapses or changes in neuroimaging (gadolinium-enhancing lesions or new/ enlarging T2 lesions). Since primary and secondary progressive MS share many pathological, clinical and imaging features, they are now considered to be part of the progressive disease spectrum.

Table 2
Some of the unusual mimics of relapsing/remitting multiple sclerosis.

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

HSV, Herpes Simplex Virus; VZV, Varicella Zooster Virus; EBV, Epstein-Barr Virus; CMV, Cytomegalovirus; HIV, Human Immunodeficiency Virus; SLE, Systemic Lupus Erythematosus; PML, Progressive Multifocal Leukoencephalopathy; CNS, Central Nervous System; HHV6, Human Herpes Virus 6; CADASIL, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy.

Similarly, progressive MS whether at onset or transitioned from relapsing forms can be classified as active or inactive based on clinical and radiological parameters. In patients with progressive disease, the disease course may be modified by clinical evidence of disease progression independent of relapses (Lublin et al., 2014).

2. Treatment of multiple sclerosis

2.1. Acute relapse

Several publications demonstrated the efficacy of Intravenous methylprednisolone (IV-MP) (Durelli et al., 1986; Milligan et al., 1987; Milanese et al., 1989). A Cochrane meta-analysis of ACTH and corticosteroids for acute MS exacerbations showed that both reduced disease progression within the first five weeks of treatment. There was a trend for better efficacy with methylprednisolone and IV treatment, but no significant difference between short (5 days) and extended (15 days) steroid treatment (Filippini et al., 2000). A more recent Cochrane meta-analysis of oral versus intravenous steroids for treatment of MS relapses showed no significant difference in efficacy between the two routes of administration. There was however a trend for higher incidence of adverse events in the oral group (Burton et al., 2012). It is generally accepted that oral prednisone taper should be used only in selected patients considered to be at an increased risk of rebound within the following 2 weeks. A second course of high dose IV-MP has been recommended by certain consensus guidelines in patients failing to improve on the initial course, but no clinical evidence is available to support such approach (Rieckmann et al., 2004). Nevertheless, it is important to recognize that the best route of administration of corticosteroids, the optimal dose and duration of treatment, and the preferred agent have yet to be firmly established.

In patients with severe residual deficits who fail to respond to IV-MP, plasmapheresis may be considered based on clinical evidence from two randomized controlled trials (RCT) (Weiner et al., 1989; Weinshenker et al., 1999). Several case series demonstrated functional neurological improvement following plasmapheresis in patients who failed to improve on IV-MP or those with severe acute exacerbations (Llufriu et al., 2009; Trebst et al., 2009; Habek et al., 2010; Magana et al., 2011). The American Academy of Neurology guideline recommends considering plasmapheresis in patients with severe relapses who fail to respond to high dose steroids (Cortese et al., 2011). Intravenous Immunoglobulin (IVIG) is not recommended for routine use in the treatment of MS relapses given the insufficient evidence. However, in patients who have contra-indications to IV-MP and plasmapheresis, IVIG (2 g/kg over 3–5 days) may be used based on the available supportive data (Visser et al., 2004; Tselis et al., 2008).

2.2. Recommendations

It is recommended to treat acute MS relapses with a 3–5 day course

Table 3
New MS phenotype classification.

Clinically Isolated Syndrome (CIS)	Relapsing-Remitting MS (RRMS)	Progressive MS***
Not-Active	Not-Active	Active* with progression**
Active*	Active*	Active* without progression**
		Not active* with progression**
		Not active* without progression** (Stable)

* Activity is defined as clinical relapses and/or MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions) assessed at least once yearly.

** Progression is determined by clinical evaluation at least once yearly.

*** Progressive disease either from onset (PP) or after an initial.

of IV Methylprednisolone (IV-MP) at a daily dose of 500–1000 mg. It is appropriate to consider plasmapheresis in the treatment of patients with severe disability who fail to respond to IV-MP.

2.3. Radiologically isolated syndrome (RIS)

RIS refers to asymptomatic patients found on routine MRI to have lesions highly suggestive of MS. The diagnosis is based on the Okuda criteria which require fulfillment of Barkhof's criteria for dissemination in space, absence of any symptoms, and lack of any other possible explanation for the radiological lesions (Okuda et al., 2009). In patients fulfilling the Okuda criteria for radiologically isolated syndrome (RIS), clinical and radiological (Brain and spine MRI) follow-up is appropriate. Current evidence does not support initiation of disease modifying therapy before the development of the first demyelinating clinical event (Okuda et al., 2014).

Recommendations: Patients with RIS should be closely followed for the development of a clinical event. Current evidence does not support initiation of DMT in RIS patients.

2.4. Clinically isolated syndrome (CIS)

2.4.1. Definition

CIS is defined as a single episode of neurological symptoms suggestive of MS, typically involving the optic nerves, brainstem/ cerebellum, spinal cord or cerebral hemispheres. The relative and absolute risk reductions for conversion to clinically definite MS over 2 years in the various randomized controlled trials (RCTs) were 50% and 15–20% respectively (Jacobs et al., 2000; Comi et al., 2001; Kappos et al., 2006; Comi et al., 2009; Comi et al., 2012). Patients with more than 9 T2 and/ or gadolinium-enhancing (Gad+) lesions had the greatest benefit (O'Connor et al., 2009). With the new revised 2017 McDonald diagnostic criteria, allowing for an earlier diagnosis of MS, the proportion of patients with CIS not fulfilling criteria for RRMS will probably be <10%, taking into account the high proportion of MS patients (90–95%) who demonstrate oligoclonal bands tested by isoelectric focusing in the CSF. In that respect, patients with CIS not fulfilling the 2017 MC Donald criteria, have either no evidence of dissemination in space (2 lesions in locations typical for MS) or negative CSF oligoclonal bands and no enhancing lesions. In both cases, we recommend a thorough review of the diagnosis to rule out any potential mimickers. In case such work-up is unrevealing and the overall clinical and radiological picture is suggestive of MS, patients with CIS and high MRI lesion load (>9 T2 lesions), and/or severe relapses with incomplete recovery, should be treated.

2.5. Relapsing remitting multiple sclerosis (RRMS)

Seven DMTs are currently approved as first-line therapy in RRMS without any restrictions: Interferon (IFN)-beta 1a IM, IFN-beta 1a SC, IFN-beta 1b SC, Peginterferon-beta 1a, GA, teriflunomide, and dimethyl fumarate (DMF). Five other DMTs are approved as first line therapy but with certain restrictions. Fingolimod and ocrelizumab are approved for initial treatment of RRMS in the USA, but can only be used in Europe for patients failing first line therapies or those with active or highly active disease from onset. Siponimod was recently approved in the USA for CIS, initial treatment of RRMS and active SPMS, 2but still awaits approval in Europe. Natalizumab is approved as second line therapy or in patients with aggressive disease from onset. Cladribine has been recently approved in Europe for treatment naïve patients with highly active disease and in both Europe and USA for patients failing first line therapies. Alemtuzumab was approved as third line therapy in the USA, and recently received a similar restriction in Europe.

2.6. Interferons & glatiramer acetate

IFN-beta modulates T and B cell activity as well as cytokine secretion, while GA modulates T regulatory cells. The use of IFN-beta and GA in RRMS is supported by class I evidence derived from several multicenter RCTs (Rice et al., 2001). They show moderate efficacy in reducing risk of relapse and disability progression by approximately 30% (Interferon beta-1b is effective in relapsing-remitting multiple sclerosis 1993; Jacobs et al., 1996; Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis 1998; Johnson et al., 1995). Furthermore, early treatment with IFN-beta 1b SC was associated with 47% reduction in the hazard ratio for all-cause mortality over 21 years as compared with initial placebo treatment (Goodin et al., 2012). The major advantage of IFN-beta and GA is their long-term safety data accumulated over more than 2 decades. Their main drawback relates to their route of administration and acute adverse events (AE) such as injection site reactions and flu-like symptoms, which have led to poor adherence (Devonshire et al., 2011). Peginterferon-beta-1a is a newly approved subcutaneous interferon. Its prolonged half-life through a process called pegylation allows for a single dosing every 2 weeks. In the ADVANCE trial, peginterferon-beta-1a reduced annualized relapse rate (ARR) by 36% and risk of disability progression by 38% with an adverse event profile similar to the rest of the Interferons (Calabresi et al., 2014). In a recent trial, double dose GA (40 mg) administered three times weekly showed similar efficacy (Khan et al., 2017)

2.7. Fingolimod

Fingolimod is a sphingosine1-phosphate receptor modulator, which inhibits lymphocyte egress from lymph nodes resulting in reduced infiltration of potentially auto-aggressive lymphocytes into the CNS (Mehling et al., 2011; Matloubian et al., 2004). Fingolimod was the first oral DMT approved for RRMS based on two phase III clinical trials (Kappos et al., 2010; Cohen et al., 2010). It reduced ARR by 55% and 52% compared to placebo and IFN-beta 1a IM respectively, and the risk of disability progression by 30% compared to placebo only (Kappos et al., 2010; Cohen et al., 2010). In a subgroup analysis of patients with highly active disease despite IFN treatment in the year preceding enrollment, fingolimod reduced ARR by 61% relative to IFN-beta 1a IM along with reduction in lesion counts and brain volume loss (Cohen et al., 2013). In a real-world study using propensity-matched data from MSBase, patients switching to fingolimod due to breakthrough disease on first line DMTs had a 26% reduction in risk of first on-treatment relapse when compared to patients switching to other first line therapies such as IFN or GA (He et al., 2015). However, careful monitoring is needed due to several safety issues including bradycardia, macular edema and infections. As of February 28, 2019, 26 cases of progressive multifocal leukoencephalopathy (PML) have been reported on fingolimod without prior natalizumab treatment, corresponding to >275,000 patients treated with fingolimod and >656,000 patient-years of exposure (Novartis data on file) (Berger et al., 2018).

2.8. Teriflunomide

Teriflunomide is a reversible inhibitor of the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH), which mediates de novo synthesis of pyrimidine in rapidly proliferating immune cells (Palmer, 2010; Claussen and Korn, 2012). Teriflunomide was the second oral DMT to receive FDA approval based on two phase III clinical trials in patients with RRMS. In the TOWER and TEMSO trials, teriflunomide at a dose of 14 mg daily, reduced ARR by 36.3% and 31%, and the risk of disability progression by 31.5% and 30% respectively when compared to placebo (Confavreux et al., 2014; O'Connor et al., 2011). When compared to IFN-beta 1a SC in a randomized rater-blinded study, teriflunomide 14 mg daily did not show any

difference in time to failure (defined as first occurrence of confirmed relapse or permanent treatment discontinuation for any cause) (Vermersch et al., 2014). Overall, Teriflunomide is well tolerated and safe with rare and mild AE including hair thinning, elevation of serum liver enzymes and mild leucopenia. Teriflunomide can be quickly cleared from the body within 11 days using oral cholestyramine or charcoal.

2.9. Dimethyl fumarate

DMF is another oral medication that has been approved for the treatment of RRMS. It is a modified fumaric acid ester which promotes anti-inflammatory and cytoprotective activities that are mediated, at least in part, by the (Nrf2) antioxidant response pathway (Linker and Gold, 2013). In an integrated analysis of the 2 phase III trials DEFINE and CONFIRM, DMF 240 mg twice daily showed a significant reduction in ARR (49%), and disability progression (32%) compared to placebo (Viglietta et al., 2015). DMF was generally safe and well tolerated; the most common AEs included flushing and gastrointestinal AE (e.g. diarrhea, nausea, vomiting). As of March 1, 2019, six cases of PML were reported in patients taking DMF corresponding to >385,000 treated patients, representing > 710,000 patient-years of exposure (Biogen data on file) (Baharnoori et al., 2016), all in the setting of prolonged moderate to severe lymphopenia. Consequently, it is advised to discontinue DMF if grade III lymphopenia (below 0.5×10^9/L) persists for more than 6 months.

2.10. Natalizumab

Natalizumab was the first approved monoclonal antibody for RRMS (Pucci et al., 2011). It is a selective adhesion molecule inhibitor that interferes with the influx of inflammatory cells into the brain by binding to the α_4 subunit of $\alpha_4\beta_1$ integrin expressed on the surface of immune cells, preventing its interaction with the vascular cell adhesion molecule (VCAM1) on the endothelial cells (Baron et al., 1993). In the phase III AFFIRM trial, natalizumab reduced the rate of clinical relapses by 68% and the risk of sustained disability progression by 42% compared to placebo (Polman et al., 2006). This was supported by extensive post marketing data, reporting improved efficacy in patients switched from first line therapies due to suboptimal response (Prosperini et al., 2012; Fernandez et al., 2012; Lanzillo et al., 2012; Lanzillo et al., 2013; Kalincik et al., 2015; Kappos, 2018). The Tysabri Observational Program (TOP) study is a multinational phase IV trial of patients initiating natalizumab with a planned 10-year follow-up. A recent analysis of the data on 6148 patients showed that patients switching from injectable or oral therapies to natalizumab had a reduction in ARR of 92.4% and 89.9% respectively, with maintained efficacy up to 10 years (Kappos, 2018). However, due to the risk of PML, estimated at around 4.22 per 1000), its use was restricted to patients failing first line therapy or those with aggressive disease. Seropositivity for JCV antibodies, prior use of immunosuppressants and duration of natalizumab treatment of more than 2 years increase the risk of PML (Sorensen et al., 2012). The prevalence of JCV antibodies in MS patients is approximately 50–60% with an 8.5–11.7% annual rate of seroconversion (Schwab et al., 2016; Alroughani et al., 2016). The risk of PML can be stratified further by quantifying serum antibody levels, measured as antibody index (AI) but only in patients without previous immunosuppression (Koendgen et al., 2016) The risk of PML remains significantly low in seronegative patients (0.1/1000), in seropositive patients with less than 2 years treatment and no prior use of immunosuppressants (0.7/1000) and in seropositive patients with AI ≤ 0.9 and no previous immunosuppressants, up to 6 years of treatment (0.6/1000). The risk however increases significantly reaching 10/1000 in seropositive patients with AI > 1.5 or prior exposure to immunosuppressants, and treated with natalizumab for more than 2 years (Idec, 2014; Plavina et al., 2014). On the other hand, natalizumab remains one of the well-tolerated DMTs with low incidence of hypersensitivity reactions (Polman et al., 2006). Recent data is showing that increased dosing interval of natalizumab up to 6–8 weeks does not affect efficacy and might decrease the risk of PML (Yamout et al., 2018a; Zhovtis Ryerson et al., 2016; Zhovtis Ryerson, 2018).

2.11. Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody that has been approved for the treatment of RRMS. Alemtuzumab targets the CD52 surface protein, which is present at high levels on T and B lymphocytes and to a lesser extent on other immune cells. In 2 phase III RCT (CARE-MS I and II), which included either treatment-naive patients or patients with relapses on IFNB/GA, alemtuzumab at a dose of 12 mg/day was associated with 55% and 49% reduction in the risk of relapse respectively compared to IFNB-1a SC. In patients with previous relapses on IFNB/GA, the risk of disability progression was reduced by 42% compared to IFNB (Cohen et al., 2012; Coles et al., 2012). In a 6 year follow-up of both trials, the significant reduction in ARR and Expanded Disability Status Scale (EDSS) progression was maintained although 55–64% of patients received no treatment beyond the first 2 years, likely due to immune reconstitution (Coles and Cohen., 2016; Fox and R.A., 2016). Besides infusion related reactions and initial increase in infection rate, the major drawback was related to delayed secondary autoimmune events with peak incidence in the third year of therapy including thyroid disease (40%), immune thrombocytopenia (1- 2%), and rare cases of anti-glomerular basement membrane disease (Fox and R.A., 2016). More adverse events have been recently reported with alemtuzumab including stroke, listeria meningitis, acute coronary syndrome and other autoimmune disorders (Buonomo et al., 2018; Ferraro et al., 2018) leading to restriction of its use to third line therapy.

2.12. Ocrelizumab

Ocrelizumab is a recombinant humanized monoclonal antibody that targets CD20 surface protein on B cells and is administered intravenously at 2 doses of 300 mg two weeks apart at onset of therapy and subsequently 600 mg every 6 months. It was recently approved by the FDA (Food and Drug Administration) and EMA (European Medicines Agency) for both RRMS and PPMS. In 2 similarly designed phase III trials (Opera I and II) involving patients with RRMS, ocrelizumab reduced ARR by 46–47% and risk of 24 weeks confirmed disability progression by 37–43% compared to IFNB-1a 44 ug 3x/week (Hauser et al., 2017). Ocrelizumab showed a good safety profile with lower incidence of serious infections compared to IFNB and a similar overall incidence of serious adverse events. A slight increase in the incidence of breast cancer was seen in the ocrelizumab arm compared to IFNB, but was within the normal range for age matched controls in different international MS registries.

2.13. Cladribine

Cladribine is a nucleoside analogue of deoxyadenosine that accumulates within cells, resulting in inhibition of DNA synthesis and repair, and subsequent apoptosis, with preferential affection of lymphocytes. It was recently approved in Europe for initial treatment of RRMS patients with high disease activity or patients failing other DMTs and in the USA for patients with RRMS failing other DMTs or with active SPMS. In a single phase III trial, Cladribine at a dose of 3.5 mg/kg, administered as oral tablets in four cycles of 5 days duration each on months 1, 2, 13 and 14 of the 2 year-long trial, reduced ARR by 58% and risk of 6 months confirmed disability progression by 47% compared to placebo. In the extension trial, patients shifted to placebo for the next 2 years showed persistent efficacy of the treatment with 77.8% and 75.6% of patients remaining relapse free during the first 2 years and

years 3 and 4 of the extension respectively, presumably due to immune reconstitution (Giovannoni et al., 2010). Accordingly, Cladribine is approved for the treatment of RRMS as 2 treatment courses during the first 2 years and no further therapy required in years 3 and 4. Cladribine showed a good safety profile with similar infection and severe infection rates compared to placebo except for slight increase in herpes zoster infections. Cladribine induces transient lymphopenia that starts recovering by 6 months post-dose. With the currently approved regimen and dosing guidelines, only 5% of patients developed Grade III lymphopenia during the extension phase and none had Grade IV lymphopenia.

2.14. Siponimod

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

2.15. Rituximab

Rituximab (RTX) is a chimeric monoclonal antibody that depletes CD20 positive B cells, currently approved in B-cell malignancies, rheumatoid arthritis, Wegener granulomatosis, and microscopic polyarthritis. The drug is widely used off-label in other systemic and neurological immune-mediated disorders such as neuromyelitis optica and myasthenia gravis (Kosmidis and Dalakas, 2010). Off-label use of RTX in MS has increased considerably following a phase 2 trial that demonstrated its positive effects in patients with RRMS (Hauser et al., 2008). Several open label or observational studies from Sweden and other parts of the world supported the efficacy and safety of RTX in comparison to other disease modifying therapies in patients with MS (Rahmanzadeh et al., 2018; Spelman et al., 2018; Naismith et al., 2010; Salzer et al., 2016). In one of these studies Alping et al. compared the efficacy of fingolimod and RTX in patients with relapsing MS following cessation of Natalizumab due to JC virus positivity. After 1.5 years, there was a significant difference between the patients receiving RTX and Fingolimod in relapse rate (1.8% vs 17.6%) and new Gd+ lesions on MRI (1.4% vs 24.2%) (Alping et al., 2016). In another observational study, Yamout et al. reported their experience with rituximab in 89 patients (59 with RRMS and 30 with PMS). They demonstrated a reduction of ARR from 1.07 at baseline to 0.11 in RRMS ($p < 0.0001$) and from 0.25 to 0.16 in PMS patients ($p = 0.593$). They also reported no evidence of clinical or radiological activity (new T2 or enhancing lesion) in 74% of their patients after one year of treatment with RTX (Yamout et al., 2018b). Although no phase III controlled studies are available, RTX share of the DMTs market is rapidly increasing in some countries like Sweden (Berntsson et al., 2018). Given the lower cost of RTX compared to other MS therapies, there is a place for its use in RRMS in countries where other alternatives are not available or affordable or in special populations such as refugees, where other appropriate options are not available. Based on the literature, the dosing of RTX is not fixed but an induction dose of 1000- 2000 mg (divided between 2 infusions in case of 2000 mg) followed by a maintenance dose of 500–1000 mg every 6 months is most commonly used. RTX is relatively well tolerated with low incidence of infusion reactions and elevation of LFTs.

2.16. Treatment algorithm for RRMS patients

Given the increasing number of available DMTs, different treatment strategies have been proposed for initiation and escalation of therapy in patients with RRMS due to lack of class 1 evidence comparative data between the newer agents. Comparing across trials with different designs and baseline characteristics is associated with inherent limitations (Zakaria, 2015). Despite advances in therapeutic trials during the last two decades, only few randomized controlled head-to-head studies were conducted (Cohen et al., 2010, 2012; Coles et al., 2012; Hauser et al., 2017). Therefore, evidence-based medicine derived from clinical studies must be supplemented by real world evidence and expert opinion in order to decide on the best therapeutic option available for an individual patient. Such evidence derived from large international or regional registries will play an increasingly important role in guiding our therapeutic options in the future. On the other hand, given the difference in mode of action of the new agents and absence of comparative data, lateral switching may be an acceptable option in patients with suboptimal response to any of the DMTs. Ideally, in a not so far future, MS therapy will be tailored to individual patient needs based on different biological and radiological biomarkers. Taking all the of the above into consideration, we developed an algorithm for the treatment of MS based on the available scientific evidence, approved FDA and EMA indication labels, and expert opinion.

2.17. Treatment naïve-patients

It is imperative to start DMTs early once the diagnosis of RRMS is established in order to reduce inflammation and secondary axonal loss in the CNS. Multiple studies have shown that early treatment might decrease the long-term accumulation of disability in patients with MS (Comi and treatment, 2006; Noyes and Weinstock-Guttman, 2013). The choice of initial therapy will depend on the extent of disease activity. Studies have shown that high disease activity (HDA) early in the course of the disease is predictive of future disability accumulation (Confavreux et al., 2003; Tintore et al., 2015). Both concepts of induction i.e. using high efficacy DMTs early in the disease course vs escalation i.e. starting with low efficacy DMTs and escalating if response is suboptimal, have been proposed for managing patients with RRMS. Unfortunately, there is no current consensus on defining highly active disease in RRMS. The following clinical and radiological features should be taken into consideration when determining if a patient has highly active disease:

- Relapse frequency in the previous year (≥2 relapses).
- Relapse severity (pyramidal/cerebellar systems involvement).
- Incomplete recovery from relapses.
- High T2 lesion load on MRI (≥10 lesions), especially with spinal or infratentorial lesions.
- Multiple Gadolinium enhancing lesions.

A subgroup of patients with high disease activity will follow a rapidly evolving aggressive course. Although no clear definition of rapidly evolving aggressive disease (READ) is agreed upon, common to all definitions is the early accumulation of disability along with high relapse frequency and highly active disease on MRI. Menon et al. defined aggressive MS as patients reaching an EDSS score of 6.0 within 5 years of disease onset or by 40 years of age (Menon et al., 2013). In their review of the British Colombia MS database, 14.3% of patients fulfilled either one of the 2 definitions, 86% of whom were relapsing remitting. Rush et al. defined aggressive MS in treatment naïve patients as 2 or more relapses with incomplete recovery in the past year (Rush et al.,

2015). The EMA definition of rapidly evolving severe disease was ≥ 2 disabling relapses in 1 year with ≥1 Gd+ lesion or significant increase in T2 lesion load. Accordingly, we defined rapidly evolving aggressive disease (READ) as the presence of 2 or more disabling relapses with incomplete recovery in the previous year and a high T2 lesion load on MRI (≥10 lesions).

2.18. Recommendations

The following DMTs can be initiated in treatment naïve patients based on class1 evidence: IFN-beta, GA, Teriflunomide, and DMF. In patients with needle phobia, or contraindications/ adverse events related to the above DMTs, fingolimod or siponimod are an acceptable alternative.

In patients with highly active disease, fingolimod, siponimod, natalizumab, ocrelizumab, or cladribine may be initiated following careful risk stratification (Serum anti-JCV antibody, prior immunosuppressant use, cardiac disease, diabetes mellitus, retinal disorders and malignancies).

In patients with rapidly evolving aggressive disease, natalizumab, ocrelizumab or alemtuzumab are recommended after careful risk stratification.

Rituximab can be used off label for HAD and READ in special populations such as refugees, or in countries where other appropriate options are not available.

In patients without evidence of breakthrough disease, but poor tolerance to first line DMTs, lateral switch to another first line DMT with a different mechanism of action or route of administration may be considered (Fig. 1).

If natalizumab is initiated in patients who are seronegative for JCV antibodies, it is recommended to test for the antibodies every 6 months. In patients on no previous immunosuppressants and who are seropositive for JCV or seroconvert during therapy with an antibody index ≥ 0.9, and in patients with prior immunosuppressant use, it is recommended to reassess benefit/risk ratio after 2 years of treatment with Natalizumab.

2.19. Suboptimal responders with breakthrough disease

This term has been interchangeably used with treatment failure, or treatment non-responders. We prefer to avoid both terms as they imply that the specific DMT being used has failed, while a certain degree of disease activity is expected with most currently available MS therapies (Freedman et al., 2009). Certain confounding factors need to be considered before labeling a patient as suboptimal responder, including poor adherence to therapy, and an adequate DMT trial for at least 6–12 months. The advent of more potent therapies has made the "No Evidence of Disease Activity' outcome measure, as defined by absence of relapses, new MRI lesions and disability progression, more attainable, and raised our level of concern to ongoing clinical or radiological disease activity in patients on DMTs.

Although we still lack a clear definition of breakthrough disease, most current criteria are based on clinical relapses, MRI activity, and accumulation of disability. With the advent of immune reconstitution therapies (IRT), such as alemtuzumab and cladribine, that require treatment for short periods of time resulting in long term durable effects, the definition of suboptimal response needs to be revised. For chronic therapies, i.e. DMTs that require continuous administration to maintain efficacy, the 2 major efforts in providing evidence-based criteria for breakthrough disease came from Rio and his group (Rio et al., 2006; Sormani et al., 2013) and the Canadian Multiple Sclerosis Working Group (CMSWG) (Freedman and Forrestal, 2008; Freedman et al., 2013). The CMSWG based their criteria on different levels of concern, reflecting increasing clinical and radiological disease activity. Low, medium, and high levels of concern were defined for clinical relapses, MRI activity, and disability progression. Applying the original CMSWG criteria to the PRISMS trial data, 89% of patients labeled as suboptimal responders at the end of the first year of therapy went on to develop significant breakthrough disease in the ensuing 3 years (Freedman and Forrestal, 2008). It is of note that high level of concern for MRI activity alone, requiring therapy change, was defined as ≥3 active lesions (enhancing and/or new T2W lesions) (Freedman et al., 2013). In a recent systematic review of all studies assessing predictors of poor response to IFN-Beta therapy, patients with

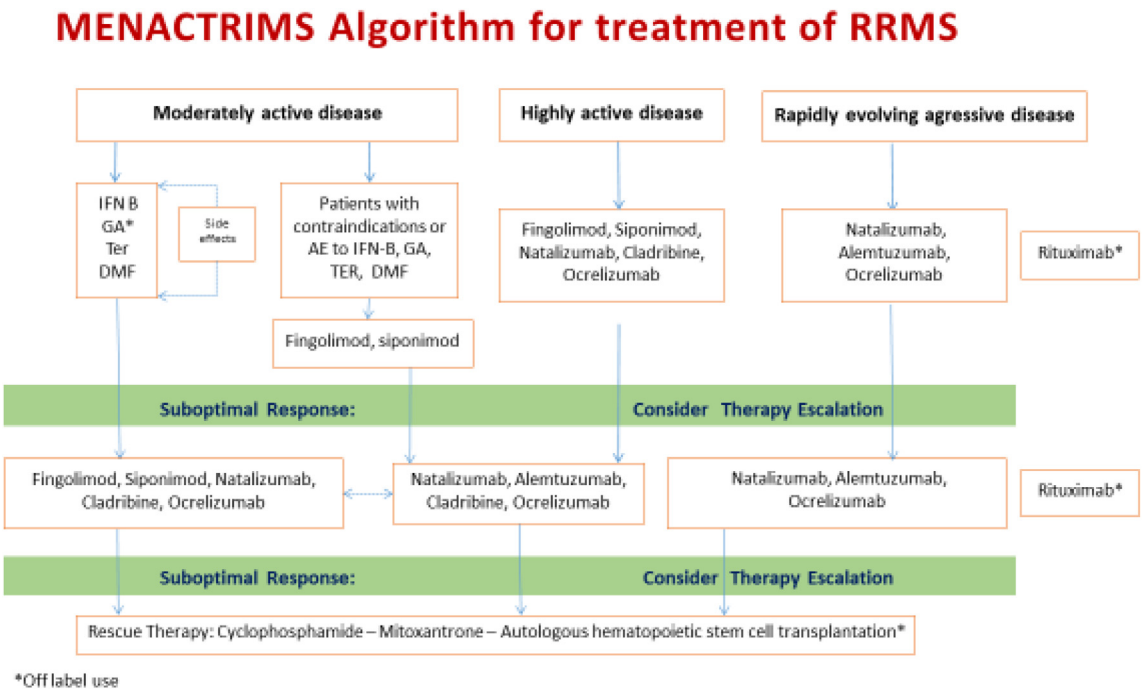

Fig. 1. Algorithm for the management of relapsing remitting MS.
IFN B: Interferon-beta, GA: Glatiramer acetate, Ter: Teriflunomide, DMF: Dimethyl fumarate.

≥ 2 new T2 or ≥1 gadolinium-enhancing lesions had significantly increased risk of both future relapses and progression (Dobson et al., 2014).

The modified Rio score was based on statistical modeling using the PRISMS trial data. It was derived from the addition of 2 scores reflecting number of relapses (no relapse = 0, 1 relapse = 1, ≥ 2 relapses = 2) and new T2W lesions (< 2 lesions = 0, ≥2 lesions = 1, if the reference MRI to compare new lesions was performed 6 months after treatment initiation) during the first year of therapy (Sormani et al., 2013). Disability progression in the subsequent 3 years was seen in 65% of patients with a modified Rio score of 2–3, and 24% of patients with a score of 0 at the end of the first year of treatment. Patients with an intermediate score of 1 were further stratified by a follow-up MRI at 18 months. The presence of ≥ 2 new T2W lesions on MRI or ≥ 1 relapse shifted them into the high-risk group (Sormani et al., 2013). It should be noted, that both efforts were designed to assess breakthrough disease in patients while on platform therapies and caution with the extrapolation of such data should be exercised.

We recommend that breakthrough disease on chronic DMTs should be considered after 1 year of treatment in patients with ≥ 1 relapse and/or disability progression or ≥2 active MRI lesions (Gd+ and/or new T2W) after 1 year of adequate treatment and using as baseline an MRI performed 6 months after treatment initiation.

The two currently available DMTs labeled as IRT are alemtuzumab and cladribine. Both are given as 2 intermittent cycles during the first and second year of treatment. They are considered to generate changes in immune regulatory networks that can be durable in some individuals and are associated with disease remission in the absence of continuous therapy (concept of drug-therapy free remission) (Ceronie et al., 2018). Suboptimal response to either drug will probably not be reliably assessed until at least 6 months following completion of the full treatment protocol i.e. 18 months after treatment initiation. Disease activity was seen in around 15% of patients on alemtuzumab in the CARE-MS I trial during the second year of treatment but did not affect long term remission from year 3 on (Wiendl et al., 2018). In a pooled CARE-MS I and CARE MS II analysis, patients with breakthrough disease requiring a third course of alemtuzumab beyond 2 years of therapy maintained a prolonged remission (TRaboulsee, 2018). Accordingly, in patients with breakthrough disease on alemtuzumab beyond the initial 2 years of treatment, a third course of this treatment is recommended before shifting to a different therapy. For cladribine there are currently no sufficient data available to substantiate the re-administration of a third course after completion of the initial 2 courses. An exception to this rule relates to few reported cases of paradoxical disease exacerbation after the first cycle of alemtuzumab, requiring a change in DMT (Wehrum et al., 2018).

2.20. Recommendation

In patients with moderately active disease and suboptimal response to first-line therapies as defined above, treatment escalation to fingolimod, siponimod, natalizumab, ocrelizumab or cladribine should be considered. It is recommended to have a reference MRI 6 months after treatment initiation for comparison (re-baseline MRI). In patients with HDA and suboptimal response to DMTs, treatment escalation to natalizumab, ocrelizumab, cladribine or alemtuzumab should be considered. In patients with READ and suboptimal response to the initial DMT, a lateral shift among alemtuzumab, ocrelizumab and natalizumab should be considered.

Alemtuzumab has class I evidence in this category of patients while effectiveness of natalizumab, ocrelizumab, cladribine and fingolimod is derived mainly from subgroup analysis of their pivotal RCTs, or post-marketing studies. The choice among them should be based on risk stratification including serum anti-JCV antibody, prior immunosuppressant use, cardiac disease, diabetes, retinal disorders, malignancies, previous autoimmune diseases, and thyroid disorders (Fig. 1).

If natalizumab is initiated in patients who are seronegative for JCV, it is recommended to test for the antibody every 6-months. In patients on no previous immunosuppressants and who are seropositive for JCV or seroconvert during therapy with an antibody index ≥0.9, and in patients with prior immunosuppressant use, it is recommended to reassess benefit/risk ratio after 2 years of treatment with Natalizumab.

In patients on IRT, breakthrough disease should be assessed at least 18 months after initiating treatment. In patients fulfilling criteria for breakthrough disease beyond the first 2 years of treatment, a third course of the DMT is recommended before shifting to another therapy, keeping in mind that data supporting such approach with cladribine is still limited.

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

In patients with evidence of breakthrough disease on any of the second line medications, a lateral switch should be considered based on the risk stratification strategy mentioned above before resorting to third line medications that are either used off-label such as cyclophosphamide and autologous hematopoietic stem cell transplantation, or have a poor safety profile such as mitoxantrone.

2.21. Treatment of progressive MS

Until recently no treatment was proven to be effective in progressive MS, but positive results are starting to emerge from newly tested drugs (Cohen et al., 2002). A Cochrane review evaluating 5 RCTS of IFN-beta in 3122 patients with SPMS concluded that IFN Beta does not prevent the development of permanent physical disability in SPMS despite reduction in the risk of relapse and short term relapse-related disability, although both IFN Beta 1a SC and IFN Beta 1b SC are currently approved in Europe for use in SPMS with relapses (La Mantia et al., 2012). Ocrelizumab was recently approved by the FDA for PPMS based on the ORATORIO trial which showed a 25% reduction in the risk of 24 week confirmed disability progression in patients on 600 mg IV twice a year as compared to placebo (Montalban et al., 2017). The patients recruited were ≤55 year old, with a disease duration ≤10–15 years and an EDSS ≤ 6.5. Such positive results cannot be extrapolated to patients not fulfilling these inclusion criteria. On the other hand a subgroup analysis showed that this effect was not statistically significant in patients without Gd+ lesions on MRI (Wollinsky, 2016). Interestingly rituximab, a chimeric anti-CD 20 monoclonal antibody failed in the OLYMPUS trial to show any superiority to placebo in patients with PPMS (Hawker et al., 2009). The main difference between the 2 trials was a younger age and shorter disease duration in ORATORIO (mean age 44.7 vs 50.1years; mean disease duration 2.9 vs 4.1 years). In another phase III trial, high dose Biotin (300 mg/day) lead to significant disability improvement at 12 months in 12.6% of patients with progressive MS (SPMS and PPMS) versus none in the placebo group (Tourbah et al., 2016). Biotin, also known as Vitamin H or B7, is a cofactor for 4 carboxylases and is postulated to enhance fatty acid synthesis and therefore myelin repair, and preserve axons by improving energy production within neurons. The trial however was limited by a small sample size (154 patients) and short follow-up (1 year). A larger trial with longer follow-up is currently ongoing to confirm those encouraging preliminary results. Siponimod is a new S1P receptor modulator, with selectivity to $S1P_1$ and $S1P_5$ receptors. In a large trial involving 1651 patients with SPMS siponimod at a dose of 2 mg/day was associated with 26% reduction in 6 months confirmed disability progression and 23.4% less brain atrophy compared to placebo, both of which were statistically significant (Kappos and A.B.-O., 2016). However, in patients without relapses in the previous 2 years or Gd+ lesions on baseline MRI, the effect on disability progression was not statistically significant. Siponimod was recently approved by the FDA for

treatment of active SPMS. Cladribine received recently the FDA approval for active SPMS based on a small Phase III double-blind cross-over trial including 48 patients treated with the intravenous form of the drug. Patients on cladribine showed a statistically significant reduction in disability progression compared to placebo-treated patients at the end of 1 year (Beutler et al., 1996). Further supportive evidence is needed to confirm those initial results.

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

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

2.22. Recommendations

Consider treatment with ocrelizumab or siponimod in patients with active SPMS, age ≤ 60 years and EDSS ≤ 6.5 (i.e. not wheelchair bound).

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

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

2.23. Pregnancy and breasfeeding

Pregnancy is associated with significant hormonal changes that affect the immune system and therefore the clinical course of MS. A significant rise in serum levels of estradiol, estriol, progesterone and cortisol, leads to a shift in the balance from a pro-inflammatory to an anti-inflammatory state. Improvement in women counseling and the advent of high efficacy DMTs have increased the proportion of women with MS attempting to get pregnant. MS per se does not appear to carry a significant risk for an adverse pregnancy outcome compared with women without MS (Tsui and Lee, 2011). A meta-analysis of 22 studies reporting on 13,144 pregnancies, showed a slight increase in the rate of caesarian sections, abortions, low birth weight and prematurity but not to a concerning level (Finkelsztejn et al., 2011).

The large prospective Pregnancy In Multiple Sclerosis (PRIMS) trial documented a 70% decrease in relapse rate during pregnancy especially in the third trimester, followed by a rebound increase relapse rate by 70% compared to preconception (Confavreux et al., 1998). These findings were confirmed by more recent studies (Finkelsztejn et al., 2011; Hughes et al., 2014). In the era of new therapeutics, it appears that the use of high efficacy DMTs may result in relapse occurrence during pregnancy, mainly associated with prolonged washout periods prior to conception (Alroughani et al., 2018). Fingolimod and natalizumab were reported to cause disease reactivation upon discontinuation in women contemplating pregnancy (Martinelli et al., 2016; Sempere et al., 2013). In all studies, the pre-pregnancy ARR was the most important predictor of postpartum relapses, stressing the importance of stabilizing the disease before attempting conception.

Despite more than 25-year experience with DMTs in MS, we still lack controlled prospective studies that assess their safety during pregnancy. All DMTs might have potential adverse events on the fetus, and the general recommendation is to discontinue treatment before attempting conception. However, such approach will increase the risk of relapse especially if conception is delayed. On the other hand, there are concerns over potential risks of stopping a beneficial DMT during pregnancy in women with highly active disease. Several measures are used in clinical practice to reduce risk of relapse if conception is delayed, but none are scientifically proven. The use of monthly infusions of high dose methylprednisolone coinciding with the menstrual cycle might mitigate such risk (Houtchens and Kolb, 2013). The use of IFNB and GA seems to be relatively safe during pregnancy based on large retrospective studies and pregnancy registries (Lu et al., 2012; Neudorfer et al., 2015). Fingolimod and mitoxantrone have both been associated with congenital anomalies in humans and are thus contraindicated in pregnancy (Karlsson et al., 2014; Pozzilli et al., 2015). Teriflunomide was associated with embryotoxicity and teratogenicity in animal studies but data from clinical trials and post-marketing setting development program, did not show any increase in the rate of congenital anomalies or spontaneous abortions in 222 pregnancies with known outcomes (Vukusic et al., 2019). A review of the clinical development program of DMF and post-marketing experience identified 69 pregnancies with exposure to the drug and known outcomes. The rate of spontaneous abortion was similar to the general population and there were no signs of teratogenicity (Gold et al., 2015). Monoclonal antibodies such as natalizumab and alemtuzumab do not cross the human placenta before week 30 of pregnancy. The Tysabri Pregnancy Exposure Registry (TPER) showed no significant adverse events in 355 prospectively followed pregnant women exposed to natalizumab (Friend et al., 2016). Natalizumab has also been used in the third trimester of pregnancy in patients with highly active disease, and induced only minor asymptomatic hematological abnormalities in the neonates (Haghikia et al., 2014). In a recent review of the alemtuzumab clinical development program, 169 pregnancies occurred in patients exposed to the drug, mostly 4 months after the last infusion (Achiron and Fox3, 2015). The rate of spontaneous abortion was similar to the general population and there were no signs of teratogenicity.

Women are generally advised to consider pregnancy after at least 1 year of disease remission irrespective of the DMT used. Although there are no recognized guidelines on when to discontinue DMTs for patients contemplating pregnancy, the panel reached a consensus on the washout periods based on the mechanism of action of the DMTs, regulatory recommendations and published studies and registries (Cree, 2013; Bove et al., 2014; Thone et al., 2017). Most experts agree that Interferons beta and glatiramer acetate may be continued till conception. This may also be the case with DMF given the short half-life, however more long-term data is needed. On the other hand, it is recommended to continue natalizumab till conception and possibly till the end of the 2nd trimester if benefit outweighs risk given that those patients had highly active disease prior to natalizumab and are at risk of disease reactivation if discontinued. If patients are treated with immune reconstitution therapies such as alemtuzumab or cladribine, it is recommended that pregnancy planning occur 4 and 6 months following the second course, respectively, in order to maximize treatment benefit while minimizing the risk of adverse events. In the case of ocrelizumab and rituximab, a 6 months interval following the last infusion is recommended before conception.

Intravenous corticosteroids are probably safe to treat relapses during pregnancy, as more recent studies did not show any increased risk of congenital malformations (Hviid and Molgaard-Nielsen, 2011). Although plasmapheresis has been used during pregnancy in severe relapses that showed no response to IV corticosteroids, the safety data is limited as the risks of hemodynamic instability and thrombophlebitis remain as potential concerns for its use (Cox et al., 2017). With respect to the use of MRI during pregnancy, a recent study reviewing 1737

pregnancies exposed to MRI during the 1st trimester did not reveal any increased risk to the fetus, but the administration of gadolinium contrast was associated with multiple complications including stillbirth (Ray et al., 2016).

Breastfeeding is recommended for all babies, including those who have parents with MS. MS does not affect the choice of how patients feed their babies. Data concerning the secretion of DMTs in breast milk and their potential risk on the baby are scarce and therefore all DMTs are generally contraindicated during breast-feeding. Although a protective effect of exclusive breastfeeding in the postpartum period was suggested by a study assessing 32 women with MS, small sample size and confounding baseline variables limited the value of this conclusion (Langer-Gould et al., 2009). A larger trial including 302 patients did not reveal such association after adjusting for disease activity prior and during pregnancy (Portaccio et al., 2011). IVIG or high dose monthly IV-MP for 3–6 months in the postpartum period might decrease the risk of relapse in women who elect to breastfeed and delay treatment with DMTs (Haas and Hommes, 2007; Hellwig et al., 2009; de Seze et al., 2004). Breastfeeding should not be undertaken within four hours of IV-MP infusion (Strijbos et al., 2015). It is generally recommended to resume high efficacy DMTs as early as possible after delivery while clinical and radiological vigilance are advised in patients who elect not to resume their DMTs given the potential risk of postpartum relapse.

2.24. PEDIATRIC MS

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

Pediatric-onset MS patients have several distinctive clinical features compared to adult patients. They experience a more aggressive disease onset with disabling clinical symptoms, multifocal relapses and higher relapse rate early in the disease course (Banwell et al., 2007; Yeh et al., 2009). A study comparing 47 pre-pubertal (<11 years) and 41 post-pubertal MS patients showed that presentation before puberty was generally more aggressive. Pre-pubertal patients were more likely to have polysymptomatic severe first attacks with motor, brainstem, sphincter and cognitive disturbances with residual sequelae (Huppke et al., 2014). Around 98% of POMS patients present with a relapsing remitting course, compared with 84% of adult patients (Banwell et al., 2009). With respect to MRI findings, POMS patients tend to have more high T2 lesion load; often located in posterior fossa and the spine with minimal disability and a tendency for the lesion to disappear after therapy (Chitnis, 2006). Brain lesions in younger children (< 11 years) tend to be large with poorly defined borders and frequently confluent at disease onset (Callen et al., 2009).

Children presenting with a typical CIS are more likely to develop MS compared to those with acute disseminated encephalomyelitis (ADEM) as their initial diagnosis. In a study of 123 children (<18 years of age) with combined retrospective and prospective follow-up (median 61.5 months), conversion from CIS to MS occurred in 26 of 67 children (38.8%), and from ADEM to MS in 4 of 47 children (8.5%) (Peche et al., 2013). Female gender, brain stem or hemispheric involvement, and fulfilling Callen MRI criteria (two of the following criteria: five or more lesions, two or more periventricular lesions, or one brainstem lesion) were found to predict the diagnosis of MS. CSF did not prove to be a good indicator for conversion (Callen et al., 2009). In a retrospective analysis, a second relapse after an initial presentation with brain stem, cerebellar or cerebral dysfunction, or multifocal CIS were strongly associated with the development of MS ($p = 0.002$). Asymptomatic brain lesions on MRI and the presence of OCBs did not predict of conversion to MS (Lee et al., 2015).

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

Many diagnostic criteria for pediatric MS have been proposed. The criteria by the Pediatric International Study Group, which were revised in 2013, have been applied in most studies (Krupp et al., 2013). The diagnosis of pediatric MS can be established after 2 non-encephalopathic clinical CNS events with presumed inflammatory cause separated by > 30 days and involving more than one CNS area, or after one non-encephalopathic episode typical of MS with MRI findings fulfilling the 2010 Revised McDonald criteria for DIS and in which a follow-up MRI shows at least one new enhancing or non-enhancing lesion fulfilling the DIT criteria, or one ADEM attack followed by a non-encephalopathic clinical event, three or more months after symptom onset, associated with new MRI lesions that fulfill the 2010 Revised McDonald criteria for DIS. In children older than 12 years, a single first event (e.g. CIS) that does not meet ADEM criteria but fulfills the 2010 revised McDonald Criteria for DIS and DIT is enough to make the diagnosis of MS (Krupp et al., 2013). Despite the addition of CSF oligoclonal bands/ IgG index as an alternative for DIT in the 2017 revised McDonald criteria (Thompson et al., 2018), it is difficult to estimate whether this addition will help to improve the diagnostic accuracy of MS in pediatric cohorts. Generally, children are less likely to have intrathecal antibody production (OCBs or an elevated IgG index) but show a high percentage of neutrophils in their CSF, suggesting prominent activation of the innate immune response (Peche et al., 2013).

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

Given the relatively high relapse rate and accumulation of disabilities at younger age, early initiation of DMTs is advised to reduce the intense inflammatory process early in the disease (Chitnis et al., 2012). Although children recover relatively well after relapses due to better neuronal plasticity, cognitive impairment is frequent (Ghezzi et al., 2010). Postponing treatment can have a negative impact on social activities and academic performance. The available data on the efficacy of current DMTs in POMS is increasing especially as few of the pivotal clinical trials are approaching their final stages. Most of this evidence was extrapolated from clinical trials in adults or based on observational or non-randomized prospective studies in pediatric cohorts evaluating primarily interferon beta and natalizumab. A recent international consensus on the use of DMTs in pediatric MS has been published in order to guide treating physicians on initiation and escalation of therapies in POMS (Chitnis et al., 2016). To date, only the results of the PARADIGMS study, a phase III, double-blind, double-dummy, randomized, multi-center trial have been published. The study evaluated the safety and efficacy of oral fingolimod vs. IFN-beta 1a in 215 children and adolescents over two years with a planned 5-year extension. Fingolimod showed a significant relative risk reduction of ARR by ~82%, and 85.7% of patients in the fingolimod group were free of confirmed relapses at Month 24 vs. 38.8% on IFN-beta 1a IM

($p < 0.001$) (Chitnis et al., 2018). Similarly, MRI parameters showed significant reduction in both T2 lesion load and T1-Gad lesions. Serious adverse events were higher in fingolimod arms (16.8% vs. 6.5%) and included seizures ($n = 4$), infections ($n = 4$), and leukopenia ($n = 2$) (Chitnis et al., 2018). Other randomized controlled trials have completed recruitment including TERIKIDS (teriflunomide), and CONNECT (dimethyl fumarate) (Jancic et al., 2016).

3. Conclusion

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

4. Authors' contributions

All authors participated as members of the panel of experts in the meeting that led to the development of the manuscript. All authors actively contributed to the discussion and the consensus reached. BY drafted the initial version of the manuscript and all authors discussed and reviewed the final version of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors received honoraria from Biologix (the distributor for Biogen Idec across the Middle East and North Africa region) for serving on their advisory board and from other pharmaceutical companies including Novartis, GSK, Bayer, Merck, Sanofi and Roche. The manuscript represents the views and opinions of the members involved in the development of the guidelines. There is no industrial or pharmaceutical support or bias in the selection of the members or the recommendations reached. This effort was sponsored and carried out under the supervision of MENACTRIMS (The Middle East and North Africa Committee for Treatment and Research In Multiple Sclerosis).

References

Achiron, A., Fox3, E.J., et al., 2015. Pregnancy outcomes in patients with active RRMS who received alemtuzumab in the clinical development program. Mult. Scler. J. 21 (S11), 581.

Al-Hashel, J., Besterman, A.D., Wolfson, C., 2008. The prevalence of multiple sclerosis in the Middle East. Neuroepidemiology 31 (2), 129–137.

Alping, P., et al., 2016. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann. Neurol. 79 (6), 950–958.

Alroughani, R., et al., 2014. Increasing prevalence and incidence rates of multiple sclerosis in Kuwait. Mult. Scler. 20 (5), 543–547.

Alroughani, R., et al., 2016. JC virus seroprevalence and seroconversion in multiple sclerosis cohort: a Middle-Eastern study. J. Neurol. Sci. 360, 61–65.

Alroughani, R., et al., 2018. Relapse occurrence in women with multiple sclerosis during pregnancy in the new treatment era. Neurology 90 (10), e840–e846.

Baharnoori, M., et al., 2016. Nonfatal PML in a patient with multiple sclerosis treated with dimethyl fumarate. Neurol. Neuroimmunol. Neuroinflamm. 3 (5), e274.

Banwell, B., et al., 2007. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. Lancet Neurol. 6 (9), 773–781.

Banwell, B., et al., 2009. Incidence of acquired demyelination of the CNS in Canadian children. Neurology 72 (3), 232–239.

Baron, J.L., et al., 1993. Surface expression of alpha 4 integrin by CD4 t cells is required for their entry into brain parenchyma. J. Exp. Med. 177 (1), 57–68.

Berger, J.R., et al., 2018. Progressive multifocal leukoencephalopathy after fingolimod treatment. Neurology 90 (20), e1815–e1821.

Berntsson, S.G., et al., 2018. Rapidly increasing off-label use of rituximab in multiple sclerosis in Sweden - outlier or predecessor? Acta Neurol. Scand. 138 (4), 327–331.

Beutler, E., et al., 1996. The treatment of chronic progressive multiple sclerosis with cladribine. Proc. Natl. Acad. Sci. U. S. A. 93 (4), 1716–1720.

Boiko, A., et al., 2002. Early onset multiple sclerosis: a longitudinal study. Neurology 59 (7), 1006–1010.

Bove, R., et al., 2014. Management of multiple sclerosis during pregnancy and the reproductive years: a systematic review. Obstet. Gynecol. 124 (6), 1157–1168.

Buonomo, A.R., et al., 2018. Risk of opportunistic infections in patients treated with alemtuzumab for multiple sclerosis. Expert Opin. Drug Saf. 17 (7), 709–717.

Burton, J.M., et al., 2012. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. Cochrane Database Syst. Rev. 12, Cd006921.

Calabresi, P.A., et al., 2014. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 13 (7), 657–665.

Callen, D.J., et al., 2009. MRI in the diagnosis of pediatric multiple sclerosis. Neurology 72 (11), 961–967.

Ceronie, B., et al., 2018. Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells. J. Neurol. 265 (5), 1199–1209.

Chitnis, T., 2006. Pediatric multiple sclerosis. Neurologist 12 (6), 299–310.

Chitnis, T., et al., 2011. Pediatric multiple sclerosis. Neurol. Clin. 29 (2), 481–505.

Chitnis, T., et al., 2012. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult. Scler. 18 (1), 116–127.

Chitnis, T., et al., 2016. Pediatric multiple sclerosis: escalation and emerging treatments. Neurology 87 (9 Suppl 2), S103–S109.

Chitnis, T., et al., 2018. Trial of Fingolimod versus interferon beta-1a in pediatric multiple sclerosis. N. Engl. J. Med. 379 (11), 1017–1027.

Claussen, M.C., Korn, T., 2012. Immune mechanisms of new therapeutic strategies in MS: teriflunomide. Clin. Immunol. 142 (1), 49–56.

Cohen, J.A., et al., 2002. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 59 (5), 679–687.

Cohen, J.A., et al., 2010. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N. Engl. J. Med. 362 (5), 402–415.

Cohen, J.A., et al., 2012. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 380 (9856), 1819–1828.

Cohen, J.A., et al., 2013. Fingolimod versus intramuscular interferon in patient subgroups from transforms. J. Neurol. 260 (8), 2023–2032.

Coles, A.J., et al., 2012. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380 (9856), 1829–1839.

Coles, A.J., Cohen, J.A., et al., 2016. on behalf of the care-Ms I investigators alemtuzumab provides durable improvements in clinical outcomes in treatment-naive patients with active relapsing remitting multiple sclerosis over 6 years in the absence of continuous treatment (CARE-MS I). Mult. Scler. J. 22 (S3), 75.

Comi, G., et al., 2001. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 357 (9268), 1576–1582.

Comi, G., 2006. Early treatment. Neurol. Sci. 27 (Suppl 1), S8–12.

Comi, G., et al., 2009. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. Lancet 374 (9700), 1503–1511.

Comi, G., et al., 2012. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. Lancet Neurol. 11 (1), 33–41.

Confavreux, C., et al., 1998. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in multiple sclerosis group. N. Engl. J. Med. 339 (5), 285–291.

Confavreux, C., et al., 2014. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 13 (3), 247–256.

Confavreux, C., Vukusic, S., Adeleine, P., 2003. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 126 (Pt 4), 770–782.

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 (3), 294–300.

Cox, J.L., Koepsell, S.A., Shunkwiler, S.M., 2017. Therapeutic plasma exchange and pregnancy: a case report and guidelines for performing plasma exchange in a pregnant patient. J. Clin. Apher. 32 (3), 191–195.

Cree, B.A., 2013. Update on reproductive safety of current and emerging disease-modifying therapies for multiple sclerosis. Mult. Scler. 19 (7), 835–843.

de Seze, J., et al., 2004. Intravenous corticosteroids in the postpartum period for reduction of acute exacerbations in multiple sclerosis. Mult. Scler. 10 (5), 596–597.

Deleu, D., et al., 2013. Prevalence, demographics and clinical characteristics of multiple sclerosis in Qatar. Mult. Scler. 19 (6), 816–819.

Devonshire, V., et al., 2011. The global adherence project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. Eur. J. Neurol. 18 (1), 69–77.

Dobson, R., et al., 2014. Assessing treatment response to interferon-beta: is there a role for MRI? Neurology 82 (3), 248–254.

Durelli, L., et al., 1986. High-dose intravenous methylprednisolone in the treatment of multiple sclerosis: clinical-immunologic correlations. Neurology 36 (2), 238–243.

Durr, F.E., Wallace, R.E., Citarella, R.V., 1983. Molecular and biochemical pharmacology of mitoxantrone. Cancer Treat. Rev. 10 (Suppl B), 3–11.

El-Salem, K., et al., 2006. Multiple sclerosis in Jordan: a clinical and epidemiological study. J. Neurol. 253 (9), 1210–1216.

Etemadifar, M., et al., 2014. Estimated prevalence and incidence of multiple sclerosis in Iran. Eur. Neurol. 72 (5–6), 370–374.

Fernandez, O., et al., 2012. Natalizumab treatment of multiple sclerosis in Spain: results of an extensive observational study. J. Neurol. 259 (9), 1814–1823.

Ferraro, D., et al., 2018. Acute coronary syndrome associated with alemtuzumab infusion in multiple sclerosis. Neurology 90 (18), 852–854.

Filippini, G., et al., 2000. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Cochrane Database Syst. Rev.(4), Cd001331.

Finkelsztejn, A., et al., 2011. What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. BJOG 118 (7), 790–797.
Fox, E.J., Brassat, D., et al., 2016. On behalf of the care-MS II investigators efficacy of alemtuzumab is durable over 6 years in patients with active relapsing-remitting multiple sclerosis and an inadequate response to prior therapy in the absence of continuous treatment (CARE-MS II). Mult. Scler. J. 22 (S3), 596.
Freedman, M.S., et al., 2009. Recognizing and treating suboptimally controlled multiple sclerosis: steps toward regaining command. Curr. Med. Res. Opin. 25 (10), 2459–2470.
Freedman, M.S., et al., 2013. Treatment optimization in MS: Canadian MS working group updated recommendations. Can. J. Neurol. Sci. 40 (3), 307–323.
Freedman, M.S., Forrestal, F.G., 2008. Canadian treatment optimization recommendations (TOR) as a predictor of disease breakthrough in patients with multiple sclerosis treated with interferon beta-1a: analysis of the prisms study. Mult. Scler. 14 (9), 1234–1241.
Friend, S., et al., 2016. Evaluation of pregnancy outcomes from the Tysabri(R) (natalizumab) pregnancy exposure registry: a global, observational, follow-up study. BMC Neurol. 16 (1), 150.
Frohman, E.M., et al., 2004. Mycophenolate mofetil in multiple sclerosis. Clin. Neuropharmacol. 27 (2), 80–83.
Ghezzi, A., et al., 2010. Cognitive impairment in pediatric multiple sclerosis. Neurol. Sci. 31 (Suppl 2), S215–S218.
Giovannoni, G., et al., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N. Engl. J. Med. 362 (5), 416–426.
Gold, R., et al., 2015. Delayed-Release dimethyl fumarate and pregnancy: preclinical studies and pregnancy outcomes from clinical trials and postmarketing experience. Neurol. Ther. 4 (2), 93–104.
Goodin, D.S., et al., 2012. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial. Neurology 78 (17), 1315–1322.
Goodin, D.S., 2014. The epidemiology of multiple sclerosis: insights to disease pathogenesis. Handb. Clin. Neurol. 122, 231–266.
Goodkin, D.E., et al., 1995. Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. Ann. Neurol. 37 (1), 30–40.
Haas, J., Hommes, O.R., 2007. A dose comparison study of ivig in postpartum relapsing-remitting multiple sclerosis. Mult. Scler. 13 (7), 900–908.
Habek, M., et al., 2010. Treatment of steroid unresponsive relapse with plasma exchange in aggressive multiple sclerosis. Ther. Apher. Dial. 14 (3), 298–302.
Haghikia, A., et al., 2014. Natalizumab use during the third trimester of pregnancy. JAMA Neurol. 71 (7), 891–895.
Hartung, H.P., et al., 2002. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet 360 (9350), 2018–2025.
Hauser, S.L., et al., 2008. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N. Engl. J. Med. 358 (7), 676–688.
Hauser, S.L., et al., 2017. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N. Engl. J. Med. 376 (3), 221–234.
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 (4), 460–471.
He, A., et al., 2015. Comparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. JAMA Neurol. 72 (4), 405–413.
Hellwig, K., et al., 2009. Immunomodulation and postpartum relapses in patients with multiple sclerosis. Ther. Adv. Neurol. Disord. 2 (1), 7–11.
Houtchens, M.K., Kolb, C.M., 2013. Multiple sclerosis and pregnancy: therapeutic considerations. J. Neurol. 260 (5), 1202–1214.
Hughes, S.E., et al., 2014. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. Mult. Scler. 20 (6), 739–746.
Huppke, B., et al., 2014. Clinical presentation of pediatric multiple sclerosis before puberty. Eur. J. Neurol. 21 (3), 441–446.
Hviid, A., Molgaard-Nielsen, D., 2011. Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ 183 (7), 796–804.
Idec, B, 2014. Natalizumab Safety Update. cited 2014 May 30]; Available from. https://medinfo.biogenidec.com.
Inshasi, J., Thakre, M., 2011. Prevalence of multiple sclerosis in Dubai, United Arab Emirates. Int. J. Neurosci. 121 (7), 393–398.
Interferon beta-1b is effective in relapsing-remitting multiple sclerosis., 1993. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB multiple sclerosis study group. Neurology 43 (4), 655–661.
Jabbour, R.A., et al., 2011. Toxocara canis myelitis: clinical features, magnetic resonance imaging (MRI) findings, and treatment outcome in 17 patients. Medicine 90 (5), 337–343.
Jacobs, L.D., et al., 1996. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The multiple sclerosis collaborative research group (MSCRG). Ann Neurol 39 (3), 285–294.
Jacobs, L.D., et al., 2000. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N. Engl. J. Med. 343 (13), 898–904.
Jancic, J., et al., 2016. Multiple sclerosis in pediatrics: current concepts and treatment options. Neurol. Ther. 5 (2), 131–143.
Johnson, K.P., et al., 1995. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The copolymer 1 multiple sclerosis study group. Neurology 45 (7), 1268–1276.
Kalincik, T., et al., 2015. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. Ann. Neurol. 77 (3), 425–435.
Kappos, L., et al., 2006. Treatment with interferon beta-1b delays conversion to clinically definite and Mcdonald MS in patients with clinically isolated syndromes. Neurology 67 (7), 1242–1249.
Kappos, L., et al., 2010. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N. Engl. J. Med. 362 (5), 387–401.
Kappos, L., et al., 2016. Safety and efficacy of siponimod (BAF312) in patients with relapsing-remitting multiple sclerosis: dose-blinded, randomized extension of the phase 2 bold study. JAMA Neurol. 73 (9), 1089–1098.
Kappos, L., et al., 2018. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 391 (10127), 1263–1273.
Kappos, L., et al., 2018. Real-world data from over 10 years in the TYSABRI® observational program: long-term safety and effectiveness of natalizumab in relapsing-remitting multiple sclerosis patients. Mult. Scler. J. 24 (2-Supplement), 489.
Kappos, L., Cree, B., et al., 2016. Efficacy and safety of siponimod in secondary progressive multiple sclerosis - Results of the placebo controlled, double-blind, phase III expand study. Mult. Scler. J. 22 (S3), 828.
Karlsson, G., et al., 2014. Pregnancy outcomes in the clinical development program of fingolimod in multiple sclerosis. Neurology 82 (8), 674–680.
Khan, O., et al., 2017. Efficacy and safety of a three-times-weekly dosing regimen of glatiramer acetate in relapsing-remitting multiple sclerosis patients: 3-year results of the glatiramer acetate low-frequency administration open-label extension study. Mult. Scler. 23 (6), 818–829.
Koendgen, H., C., I., Sperling, B., Bloomgren, G., Haddock, B., Richman, S., Ho, P.-.R., Campbell, N., 2016. New algorithm to estimate risk of natalizumab-associated progressive multifocal leukoencephalopathy (PML) in antiJCV antibody positive patients: analyses of clinical trial data to provide further temporal precision and inform clinical practice. Mult. Scler. J. 22 (S3), 659.
Kosmidis, M.L., Dalakas, M.C., 2010. Practical considerations on the use of rituximab in autoimmune neurological disorders. Ther. Adv. Neurol. Disord. 3 (2), 93–105.
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. Mult. Scler. 19 (10), 1261–1267.
La Mantia, L., et al., 2012. Interferon beta for secondary progressive multiple sclerosis. Cochrane Database Syst. Rev. 1, CD005181.
Langer-Gould, A., et al., 2009. Exclusive breastfeeding and the risk of postpartum relapses in women with multiple sclerosis. Arch. Neurol. 66 (8), 958–963.
Lanzillo, R., et al., 2012. Natalizumab vs interferon beta 1a in relapsing-remitting multiple sclerosis: a head-to-head retrospective study. Acta Neurol. Scand. 126 (5), 306–314.
Lanzillo, R., et al., 2013. Natalizumab is effective in multiple sclerosis patients switching from other disease modifying therapies in clinical practice. Neurol. Sci. 34 (4), 521–528.
Lee, C.G., et al., 2015. The natural course of clinically isolated syndrome in pediatric patients. Brain Dev. 37 (4), 432–438.
Link, H., Huang, Y.M., 2006. Oligoclonal bands in multiple sclerosis cerebrospinal fluid: an update on methodology and clinical usefulness. J. Neuroimmunol. 180 (1–2), 17–28.
Linker, R.A., Gold, R., 2013. Dimethyl fumarate for treatment of multiple sclerosis: mechanism of action, effectiveness, and side effects. Curr. Neurol. Neurosci. Rep. 13 (11), 394.
Llufriu, S., et al., 2009. Plasma exchange for acute attacks of CNS demyelination: predictors of improvement at 6 months. Neurology 73 (12), 949–953.
Lu, E., et al., 2012. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. Neurology 79 (11), 1130–1135.
Lublin, F.D., et al., 2014. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83 (3), 278–286.
Magana, S.M., et al., 2011. Beneficial plasma exchange response in central nervous system inflammatory demyelination. Arch. Neurol. 68 (7), 870–878.
Martinelli Boneschi, F., et al., 2013. Mitoxantrone for multiple sclerosis. Cochrane Database Syst. Rev. 5, CD002127.
Martinelli, V., et al., 2016. Recurrent disease-activity rebound in a patient with multiple sclerosis after natalizumab discontinuations for pregnancy planning. Mult. Scler. 22 (11), 1506–1508.
Matloubian, M., et al., 2004. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature 427 (6972), 355–360.
McDonald, W.I., et al., 2001. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann. Neurol. 50 (1), 121–127.
Mehling, M., Kappos, L., Derfuss, T., 2011. Fingolimod for multiple sclerosis: mechanism of action, clinical outcomes, and future directions. Curr. Neurol. Neurosci. Rep. 11 (5), 492–497.
Menon, S., et al., 2013. Characterising aggressive multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 84 (11), 1192–1198.
Milanese, C., et al., 1989. Double-blind randomized trial of ACTH versus dexamethasone versus methylprednisolone in multiple sclerosis bouts. Clinical, cerebrospinal fluid and neurophysiological results. Eur. Neurol. 29 (1), 10–14.
Miller, D.H., et al., 2008. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult. Scler. 14 (9), 1157–1174.
Milligan, N.M., Newcombe, R., Compston, D.A., 1987. A double-blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis: 1. clinical effects. J. Neurol. Neurosurg. Psychiatry 50 (5), 511–516.
Montalban, X., et al., 2017. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N. Engl. J. Med. 376 (3), 209–220.
Naismith, R.T., et al., 2010. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. Neurology 74 (23), 1860–1867.

Neudorfer, O., M. S.-W., P.K., Coyle, B., et al., 2015. The Glatiramer acetate pregnancy database. Mult. Scler. J. 21 (S11), 793.
Noyes, K., Weinstock-Guttman, B., 2013. Impact of diagnosis and early treatment on the course of multiple sclerosis. Am. J. Manag. Care 19 (17 Suppl), s321–s331.
O'Connor, P., et al., 2011. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N. Engl. J. Med. 365 (14), 1293–1303.
O'Connor, P., Kinkel, R.P., Kremenchutzky, M., 2009. Efficacy of intramuscular interferon beta-1a in patients with clinically isolated syndrome: analysis of subgroups based on new risk criteria. Mult. Scler. 15 (6), 728–734.
Okuda, D.T., et al., 2009. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. Neurology 72 (9), 800–805.
Okuda, D.T., et al., 2014. Radiologically isolated syndrome: 5-year risk for an initial clinical event. PLoS ONE 9 (3), e90509.
Palmer, A.M., 2010. Teriflunomide, an inhibitor of dihydroorotate dehydrogenase for the potential oral treatment of multiple sclerosis. Curr. Opin. Investig. Drugs 11 (11), 1313–1323.
Peche, S.S., et al., 2013. A long-term follow-up study using IPMSSG criteria in children with CNS demyelination. Pediatr. Neurol. 49 (5), 329–334.
Plavina, T., et al., 2014. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann. Neurol. 76 (6), 802–812.
Polman, C.H., et al., 2006. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N. Engl. J. Med. 354 (9), 899–910.
Polman, C.H., et al., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the Mcdonald criteria. Ann. Neurol. 69 (2), 292–302.
Portaccio, E., et al., 2011. Breastfeeding is not related to postpartum relapses in multiple sclerosis. Neurology 77 (2), 145–150.
Poser, C.M., et al., 1983. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann. Neurol. 13 (3), 227–231.
Pozzilli, C., Pugliatti, M., Paradig, M.S.G., 2015. An overview of pregnancy-related issues in patients with multiple sclerosis. Eur. J. Neurol. 22 (Suppl 2), 34–39.
Prosperini, L., et al., 2012. Escalation to natalizumab or switching among immunomodulators in relapsing multiple sclerosis. Mult. Scler. 18 (1), 64–71.
Pucci, E., et al., 2011. Natalizumab for relapsing remitting multiple sclerosis. Cochrane Database Syst. Rev.(10), CD007621.
Rahmanzadeh, R., et al., 2018. B cells in multiple sclerosis therapy-A comprehensive review. Acta Neurol. Scand. 137 (6), 544–556.
Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis., 1998. PRISMS (Prevention of relapses and disability by interferon beta-1a subcutaneously in multiple sclerosis) study group. Lancet 352 (9139), 1498–1504.
Ray, J.G., et al., 2016. Association between MRI exposure during pregnancy and fetal and childhood outcomes. JAMA 316 (9), 952–961.
Renoux, C., et al., 2007. Natural history of multiple sclerosis with childhood onset. N. Engl. J. Med. 356 (25), 2603–2613.
Rice, G.P., et al., 2001. Interferon in relapsing-remitting multiple sclerosis. Cochrane Database Syst. Rev.(4), CD002002.
Rieckmann, P., et al., 2004. Escalating immunotherapy of multiple sclerosis–new aspects and practical application. J. Neurol. 251 (11), 1329–1339.
Rio, J., et al., 2006. Defining the response to interferon-beta in relapsing-remitting multiple sclerosis patients. Ann. Neurol. 59 (2), 344–352.
Rovira, A., et al., 2015. Evidence-based guidelines: magnims consensus guidelines on the use of MRI in multiple sclerosis-clinical implementation in the diagnostic process. Nat. Rev. Neurol. 11 (8), 471–482.
Rubin, J.P., Kuntz, N.L., 2013. Diagnostic criteria for pediatric multiple sclerosis. Curr. Neurol. Neurosci. Rep. 13 (6), 354.
Rush, C.A., MacLean, H.J., Freedman, M.S., 2015. Aggressive multiple sclerosis: proposed definition and treatment algorithm. Nat. Rev. Neurol. 11 (7), 379–389.
Salzer, J., et al., 2016. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. Neurology 87 (20), 2074–2081.
Schumacker, G.A., et al., 1965. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. Ann. N. Y. Acad. Sci. 122, 552–568.
Schwab, N., et al., 2016. Therapy with natalizumab is associated with high JCV seroconversion and rising JCV index values. Neurol. Neuroimmunol. Neuroinflamm. 3 (1), e195.
Selmaj, K., et al., 2013. Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study. Lancet Neurol. 12 (8), 756–767.
Sempere, A.P., Berenguer-Ruiz, L., Feliu-Rey, E., 2013. Rebound of disease activity during pregnancy after withdrawal of fingolimod. Eur. J. Neurol. 20 (8), e109–e110.
Sorensen, P.S., et al., 2012. Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. Mult. Scler. 18 (2), 143–152.
Sormani, M.P., et al., 2013. Scoring treatment response in patients with relapsing multiple sclerosis. Mult. Scler. 19 (5), 605–612.
Spelman, T., et al., 2018. Comparative effectiveness of rituximab relative to IFN-beta or glatiramer acetate in relapsing-remitting MS from the SWEDISH MS registry. Mult. Scler. 24 (8), 1087–1095.
Strijbos, E., et al., 2015. High-dose methylprednisolone for multiple sclerosis during lactation: concentrations in breast milk. Mult. Scler. 21 (6), 797–798.
Thompson, A.J., et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the Mcdonald criteria. Lancet Neurol. 17 (2), 162–173.
Thone, J., et al., 2017. Treatment of multiple sclerosis during pregnancy - safety considerations. Expert Opin. Drug Saf. 16 (5), 523–534.
Tintore, M., et al., 2015. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 138 (Pt 7), 1863–1874.
Tourbah, A., et al., 2016. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: a randomised, double-blind, placebo-controlled study. Mult. Scler. 22 (13), 1719–1731.
TRaboulsee, A.e.a., 2018. Additional courses of alemtuzumab improved clinical and MRI outcomes in pooled care-MS I and II patients with disease activity after two courses: analysis of patients who received ≥3 courses. Mult. Scler. 24 (S2), 517.
Trebst, C., et al., 2009. Plasma exchange therapy in steroid-unresponsive relapses in patients with multiple sclerosis. Blood. Purif. 28 (2), 108–115.
Trojano, M., et al., 2011. Natural history of multiple sclerosis: have available therapies impacted long-term prognosis? Neurol. Clin. 29 (2), 309–321.
Tselis, A., et al., 2008. Treatment of corticosteroid refractory optic neuritis in multiple sclerosis patients with intravenous immunoglobulin. Eur. J. Neurol. 15 (11), 1163–1167.
Tsui, A., Lee, M.A., 2011. Multiple sclerosis and pregnancy. Curr. Opin. Obstet. Gynecol. 23 (6), 435–439.
Vermersch, P., et al., 2014. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult. Scler. 20 (6), 705–716.
Viglietta, V., et al., 2015. Efficacy of delayed-release dimethyl fumarate in relapsing-remitting multiple sclerosis: integrated analysis of the phase 3 trials. Ann. Clin. Transl. Neurol. 2 (2), 103–118.
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 (1), 89–91.
Vukusic, S., et al., 2019. Pregnancy outcomes in patients with multiple sclerosis treated with teriflunomide: clinical study data and 5 years of post-marketing experience. Mult. Scler 1352458519843055.
Wehrum, T., et al., 2018. Activation of disease during therapy with alemtuzumab in 3 patients with multiple sclerosis. Neurology 90 (7), e601–e605.
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 (9), 1143–1149.
Weinshenker, B.G., et al., 1999. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann. Neurol. 46 (6), 878–886.
Wiendl, H., Calabresi, P.A., Meuth, S.G., 2018. Defining response profiles after alemtuzumab: rare paradoxical disease exacerbation. Neurology 90 (7), 309–311.
Wollinsky, J.e.a., 2016. Efficacy of ocrelizumab in patients with PPMS with and without T1 gadolinium-enhancing lesions at baseline in a phase III, placebo-controlled trial. Mult. Scler. 22 (S1), 63–64.
Yamout, B., et al., 2013. Consensus guidelines for the diagnosis and treatment of multiple sclerosis. Curr. Med. Res. Opin. 29 (6), 611–621.
Yamout, B.I., et al., 2018b. Safety and efficacy of rituximab in multiple sclerosis: a retrospective observational study. J. Immunol. Res. 2018, 9084759.
Yamout, B.I., et al., 2018a. Efficacy and safety of natalizumab extended interval dosing. Mult. Scler. Relat. Disord. 24, 113–116.
Yeh, E.A., et al., 2009. Pediatric multiple sclerosis. Nat. Rev. Neurol. 5 (11), 621–631.
Zakaria, M., 2015. Smoke and mirrors: limited value of relative risk reductions for assessing the benefits of disease-modifying therapies for multiple sclerosis. Mult. Scler. Relat. Disord. 4 (3), 187–191.
Zephir, H., et al., 2004. Treatment of progressive forms of multiple sclerosis by cyclophosphamide: a cohort study of 490 patients. J. Neurol. Sci. 218 (1–2), 73–77.
Zhovtis Ryerson, L., et al., 2016. Extended interval dosing of natalizumab in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 87 (8), 885–889.
Zhovtis Ryerson, L., 2018. Natalizumab extended interval dosing is associated with a reduction in progressive multifocal leukoencephalopathy (PML) risk in the touch® registry. Mult. Scler. 24 (1–Supplement), 121–122.