NEW TREATMENT PARADIGMS IN THE MANAGEMENT OF MULTIPLE SCLEROSIS

Abstract

Younger adults (ages 20-30), with a slight female predominance, are the global population most impacted by multiple sclerosis (MS). A full understanding of this progressive and disabling acquired autoimmune disease of the central nervous system (CNS) still eludes the medical profession. Most likely caused by complex gene-environment interactions, with the latter being the more significant factor, recent advances in MS diagnosis and treatment are translating into earlier detection and better treatment outcomes. This opens the potential for long-term remission and even cure in small subsets of affected individuals, although long-term outcomes of the emerging disease-modifying therapies (DMTs) are currently largely unknown. This article will highlight some of the new paradigms in understanding and managing MS and associated implications for risk assessment.

Challenging Previously Held Views

MS is a chronic condition of variable course in which the patient's immune system attacks the nerve fibers (axons) of the patient's central nervous system (CNS). Diagnosis is based on the most recent (2017) revision of the McDonald Criteria for the Diagnosis of Multiple Sclerosis, which was first developed in 2001 and is reviewed and updated every five years.[1] While there are many nuances in the diagnostic process, at the most basic level, confirming MS requires evidence of CNS damage that is both disseminated in time (DIT) and in space (DIS), i.e., being able to show a timeline for the damage and where in the nervous system it occurred.

Table 1 shows the combination of clinical findings, imaging and laboratory tests used by the McDonald Criteria to confirm a diagnosis.

A finding of oligoclonal bands in cerebrospinal fluid (CSF) tests can now be used to demonstrate DIT and confirm a diagnosis, as this indicates intrathecal antibody production. This finding can also be used to assess treatment response and prognosis, as it has been shown to associate with higher risk of a subsequent MS attack.[1]

Advances in magnetic resonance imaging (MRI) technology, including volumetric and functional imaging, are also expanding the role of imaging in MS beyond its current clinical application of disease activity estimation to include assessment of treatment response and long-term clinical outcomes.

Recently, researchers have trained a machine learning algorithm to predict the progression of disability and possible responses to treatment based on an analysis of early MRI abnormalities.[2] The research defined three MS subtypes from the results, with one subtype showing the highest risk of progression and rate of relapse, yet also demonstrating the most significant treatment response. This data-driven approach and similar insights into what influences progression has the potential to be used in future clinical

ABOUT THE AUTHOR

Dr. Heather Lund
hlund@rgare.com

Heather M. Lund, MBBCh, is Chief Medical Officer – Asia at RGA Reinsurance Company. She provides medical consultation expertise and technical assistance for reinsurance underwriting and claims assessment, supporting actuarial business development, marketing, and pricing teams across the Asia region. A native of South Africa, Heather's Bachelor of Medicine, Bachelor of Surgery (MBBCh) degree is from the University of the Witwatersrand in Johannesburg. Her background is in family medicine, with a special interest in maternal health. She is a frequent contributor to medical publications and has also served on program committees of the International Committee for Insurance Medicine (ICLAM) and the Academy of Insurance Medicine in Asia (AIMA).

Table 1: The 2017 McDonald Criteria

Clinical Episodes	Objective Clinical Lesions	Additional Requirements to Satisfy Diagnosis
2 or more	2 or more	None
2 or more	1	Dissemination in Space (evidenced either by MRI or via second clinical attack implicating a different CNS site)
1	2 or more	Dissemination in Time (evidenced by MRI, CSF test, or via second clinical attack)
1	1	Dissemination in Space AND Time (evidenced by MRI, CSF test, or via second clinical attack)
0/Progressive at Onset	N/A	• One year of disease progression PLUS two of the following three: ◦ DIS in the brain (periventricular, cortical or juxtacortical, or infratentorial regions) ◦ DIS in the spinal cord ◦ Positive CSF

Source: Thompson AJ, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald Criteria. Lancet Neurology[1]

trials to stratify patients, individualize treatment, and might even be a crucial step toward finding new treatments.

Current limitations of treatment stratification in MS are due partly to the lack of clear pathophysiological boundaries of the currently identified clinical phenotypes.

The clinical distinctions made among the three subtypes are:

- Relapsing remitting MS (RRMS): This is the most commonly encountered form. It is characterized by periods of stability (remission) followed by episodes of symptom exacerbations (relapses). A second clinical attack typically occurs within the first two years after an untreated RRMS episode.
- Secondary progressive MS (SPMS): More than half of RRMS patients advance into SPMS 10 to 15 years after onset. In SPMS, symptoms worsen progressively without remission and disability accumulates.
- Primary progressive MS (PPMS): This is MS's most rapidly progressive form. It is characterized by symptoms that gradually and steadily worsen over time from initial presentation without relapses and remissions, and comprises about five to 15% of all cases.

Two related conditions along the diagnostic continuum are also described:

- Clinically isolated syndrome (CIS): This would be a patient's first clinically recorded inflammatory demyelinating CNS event. Such events do not generally fulfill all the diagnostic criteria for MS. However, they may indicate a patient's possible predisposition toward the development of clinically definite MS. The cumulative risk of developing the disease after a single episode of optic neuritis was assessed in a small Italian study in 2000. The study suggested a probability of 13% after two years, 30% after four years, 38% after six years, and 49% after eight and ten years.[3] Contemporary ophthalmological and neurological management would therefore most likely include an MRI scan after a first episode of optic neuritis.
- Radiographically isolated syndrome (RIS): In this, brain lesions characteristic of MS are incidentally found in MRIs performed for other conditions in asymptomatic patients.

All of these clinical distinctions are currently being challenged. Additionally, the MS diagnostic continuum is expanding to include preclinical (asymptomatic) or prodromal (early signs and symptoms, such as RIS) disease. This is becoming increasingly important for

insurers, as those diagnosed as having RIS are not eligible for treatment according to current guidelines, yet one study found that approximately one-third of these individuals progress to MS within five years.[4]

Furthermore, neurodegeneration can be present from the clinical onset of MS, with progressive atrophy already often seen on early MRI scans in MS patients. This begs the question whether some or all MS patients might benefit from early treatment intervention that could limit or prevent end-organ damage.

On the opposite end of the disease spectrum, only limited treatments are available for those with PPMS. Its rapid progression has to date made it difficult to assess treatment effects and has thus produced disappointing clinical trial results. In some instances, PPMS diagnoses have been reclassified to another subtype so that the patient could obtain treatment, challenging the reasonability of the current stratification of disease states.

Thus, similar to other neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, a shift toward preclinical screening and diagnosis of MS for at-risk groups will need to be considered both from the potential of studying preventive strategies (although these may take several years to produce meaningful results) and from a clinical and disease outcome perspective.

This shift could impact all insurance product lines quite significantly. Mortality, morbidity, and healthcare benefits would each be impacted differently. Although mortality and disability could show improvements over time, critical illness and health products would potentially be the most adversely affected by any fundamental change in the diagnostic and/or disease management approach.

Trends in Outcomes and Current Treatment Eligibility

Treatment of MS used to focus only on episodes of disease relapse. In recent years, newer approaches using disease-modifying therapies (DMTs) earlier in the course have increasingly been employed and have improved outcomes. As mentioned, quantifying treatment efficacy in terms of clinical trial outcomes has been challenging, owing to the inherent limitations of adequately measuring long-term disease outcomes using short-term studies, but analyses of trends seen in long-established MS registries have indicated secular improvements in both patient longevity and functional outcomes.

Although predating many of the newer treatment advances, a 2015 population-based Canadian study found that survival improved over a 27-year time period for the MS population but remained somewhat lower than for a matched population without MS.[5] Median survival from birth in the MS population was 75.9 years vs. 83.4 years in the matched population. The impact of comorbidity was also considered and was associated with increased mortality as expected, but not greater than in the matched study population.

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In the long-term EPIC (expression/genomics, proteomics, imaging, and clinical) single-center prospective observational cohort, originally set up at the University of California in San Francisco in 2004, individuals with RRMS were recently found to transition to SPMS at a median of 16.8 years after disease onset.[6] Outcomes in this contemporary and actively managed cohort are currently assessed using clinical measures (relapses), radiographic measures (MRI activity), and progression of disability using various disability scales, the most common being the Kurtzke Expanded Disability Severity Scale (EDSS).

In a very recent study, the effect of DMTs on long-term disability in people with MS was assessed using observational data from the MSBase registry, an international registry which focuses on the study of MS and other neurological diseases.[7] Comparing disability outcomes over 15 years or more of follow-up during periods of DMT treatment versus no treatment in patients with RRMS, worsening disability was approximately 20%

lower for treated patients, with a 67% reduction in the need for a walking aid.

Evidence supports the notion that everyone with a diagnosis of RRMS should be treated with DMT, and that earlier treatment is associated with better outcomes.

Treatment for other clinical phenotypes includes for those with CIS but who also have additional clinically silent lesions in the brain or spinal cord imaging. This is in line with an overall trend toward treating those with CIS to delay onset of clinically definite MS, those with SPMS who have clinically active disease or new lesions on imaging, and those with PPMS who are younger (age ≤55 years) or are showing active disease on MRIs.

When treatment is indicated, shared decision-making is advocated, and individualized treatment plans are becoming the norm.

Contemporary MS management requires a broad, multilayered approach to controlling acute attacks, managing disease progression, and treating debilitating symptoms.

Rising to the Treatment Challenge

In MS, regardless of the clinical disease type, inflammation leads to nerve cell damage with subsequent axonal damage (axonal transection) and demyelinating sclerotic plaque formation, which disrupts nerve conduction throughout the CNS leading to eventual and irreversible neurological damage. The goals of treatment include suppression of inflammation and active disease, and a deceleration of progressive disease with concomitant preservation of function. An ultimate aspiration would be cure.

Contemporary MS management requires a broad, multilayered approach to controlling acute attacks, managing disease progression, and treating debilitating symptoms. Treatments can be classified into DMTs (MS-specific) and symptomatic (non-MS-specific) therapies.

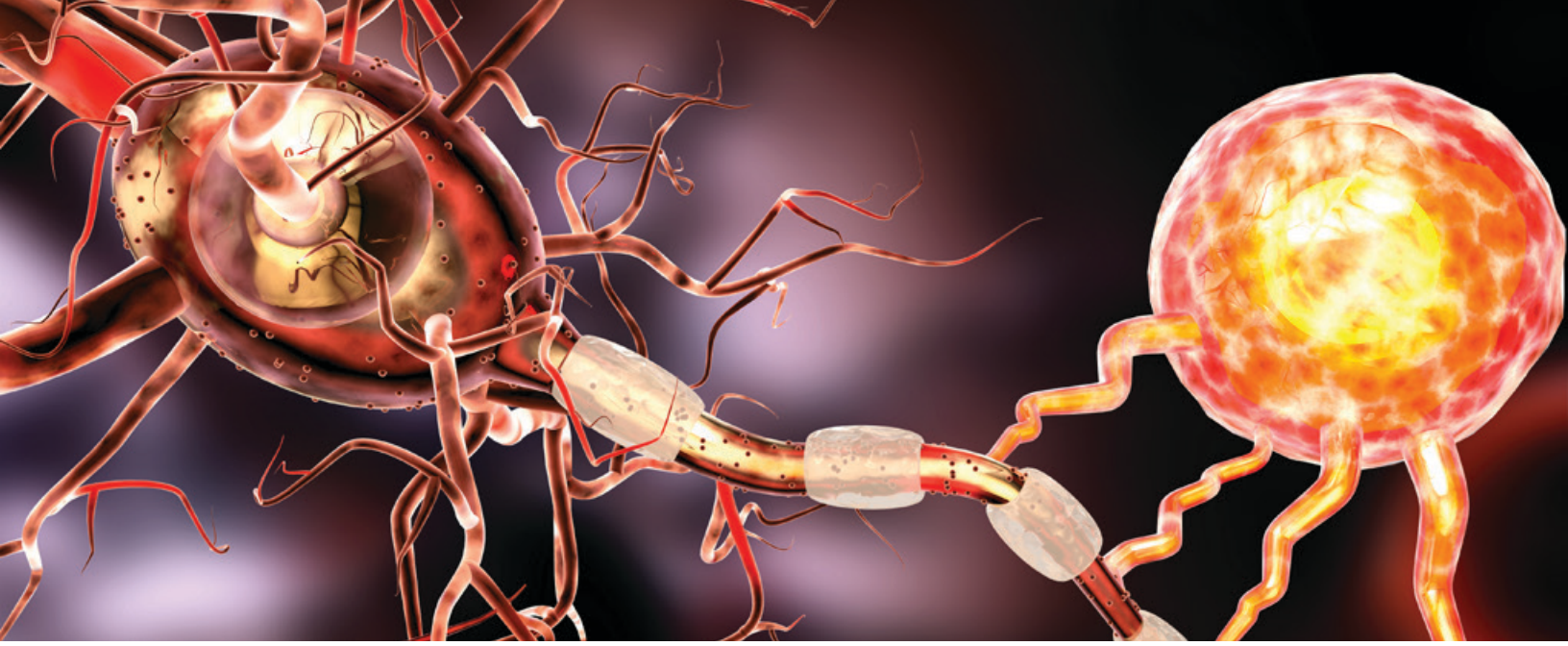
Many different classes of MS-specific DMTs are available, each of which has different mechanisms of action and routes of administration. Table 2 (on p.12) lists the currently approved DMTs, their mechanisms of action, routes of administration, relative potency, brief description of major adverse effects and monitoring requirements, and current indications.

The first DMT was approved almost 30 years ago. Before this, there were no known drug treatment options that affected MS disease progression at all. Since then, several DMTs have been approved, including nine within the last two years alone.

New therapies that work at various points along the disease continuum have broadened the landscape for significant improvements. DMTs for MS have been found to decrease the frequency of relapses, reduce the number of MRI findings, and reduce patient short-term disability. Although caution is advised when interpreting the variation across populations and time periods studied, treatment with DMTs can reduce the annualized relapse rate (a measure of treatment efficacy) by 29% to 68%, compared with placebo or comparator drug.[8] Data are limited, but some DMTs may even slow the underlying neurodegenerative (atrophy) process, although the overall impact of these newer modalities may not yet be fully appreciated.

There has also been a shift in understanding the role B-cells may play in the immunopathogenesis of MS away from a purely T-cell-mediated pathogenesis, hence the introduction of B-cell-depleting DMTs.

As with many other diseases, treatment risks and benefits must be considered before choosing the appropriate therapeutic approach. For MS, this could involve starting with less potent DMTs and stepping up to a more potent medication as disease activity requires. The alternative is to begin with a more potent DMT as first-line therapy, which although not confirmed in any randomized trial as yet, might be the preferred option in terms of tolerability and adherence as well as reducing the risk of SPMS conversion and permanent disability. This is the big debate emerging in MS management.



An emerging MS treatment goal and outcome measure is NEDA (no evidence of disease activity). Achieving NEDA means that for MS patients currently being treated with drugs, the disease is stable (i.e., no new relapses, no progression in disability, and no new or enlarging lesions showing up on MRIs). Long-term persistence of NEDA at this time is still unknown and probably unlikely, and clinical relapses after a period of NEDA might represent a later stage of overall disease activity.[6, 9] This goal has led to treatment escalation earlier in the disease course or early treatment with more potent therapies as first-line treatments.

NEDA is currently defined and evidenced by these clinical parameters:

- NEDA 1 and 2 – absence of relapses and disease progression
- NEDA 3 – adds no clinical activity and no inflammatory MRI activity
- NEDA 4 and 5 – adds normalizing MRI atrophy, and normal biomarker levels (i.e., normal CSF neurofilament levels)

Types of Treatments

Some regimes start with oral therapies, which have intermediate efficacy and risk. Women with MS who wish to conceive would need to be appropriately counseled and treated, given the teratogenic potential of many of the DMTs.

Disease-specific DMTs

- Maintenance/escalation therapy: active and ongoing therapy scaled over time that are either immunomodulatory (interferon beta, glatiramer acetate, teriflunamide) or immunosuppressive (fingolimod, or monoclonal antibodies [mAb] such as natalizumab and ocrelizumab).
- Immune reconstitution therapy: short-course therapy resulting in long-term, qualitative immune function changes and disease remission (which is the closest to a potential cure). Treatments include alemtuzumab, HSCT (impacting the innate and adaptive immune systems), and cladribine (impacting the adaptive immune system).
- PPMS-specific therapy: Ocrelizumab is currently the only approved DMT for treatment of PPMS. As a B-cell depleting treatment, it is thought specifically to reduce B-cell-mediated inflammation implicated in the neurodegenerative process. Premedication with a corticosteroid and antihistamine are required.

  Treatment for mild relapses may not be necessary, but high-dose systemic steroids are used for moderate to severe relapses. Plasma exchange is also sometimes tried for relapses that are either severe or refractory to steroid treatment.

Symptomatic and other non-DMS treatments

As MS progresses, supportive treatments may be needed for CNS damage or associated conditions such

as bladder dysfunction, neuropathic pain, cognitive or gait impairments, psychiatric comorbidities, or sleep disruption. Comorbid conditions worsen the trajectory and associated disability in MS. Treatment, especially of associated depression or anxiety disorders (present in up to 50% of those with MS), leads to improved patient quality of life and usually correlates with better treatment adherence.

Supervised lifestyle and wellness modifications seem also to impact outcomes positively, although evidence for this is modest. Smoking cessation must be strongly encouraged, as smoking has a negative impact on prognosis. Very little robust evidence exists for the impact of dietary modifications in MS. Psychological support is crucial throughout and rehabilitation is especially necessary for progressive disease.

Multidisciplinary care, although not formally studied in randomized trials, is intuitively advisable wherever possible, given the complex nature of the disease and its multiple associated comorbidities.

Table 2: DMTs and Corresponding Considerations, Indications

DMT	Mechanism of action	Class	Efficacy (generalized from clinical evidence)	Administration route	Required monitoring	Rare aftereffect	Indication
Fingolimod Siponimod Ozanimod	Immuno-suppressive, can cross blood-brain barrier	Sphingosine 1-phosphate (S1P) receptor modulators	High	Oral	CBC, LFT, U&E, TFT, eye and skin examination	Bradycardia, heart block, infections, macular edema	RRMS, CIS, SPMS
Interferon beta	Immuno-modulatory	Interferons	Moderate	SC or IM	CBC, LFT, U&E, TFT ,	Liver toxicity	RRMS, CIS, SPMS
Glatiramer acetate	Immuno-modulatory	Amino acid copolymer	Moderate	SC	CBC, LFT (sometimes none)	Skin necrosis	RRMS, CIS, SPMS
Teriflunomide	Immuno-modulatory	Pyrimidine synthesis inhibitor	Moderate	Oral	CBC, LFT, U&E	Teratogenicity, hepatotoxicity	RRMS, CIS, SPMS
Dimethyl fumarate; Diroximel fumarate	Pleiotropic	Fumarates	High	Oral	CBC, LFT, U&E	Infections, liver toxicity	RRMS, CIS, SPMS
Cladribine	Immune reconstitution	Purine analogue	Very high	Oral	CBC, U&E, TFT, age-appropriate cancer screenings,	Malignancy, infections, and teratogenicity	RRMS, SPMS
Ocrelizumab (Anti-CD20) Ofatumumab (Anti-CD20) Natalizumab (Anti-α4 integrin receptor) Alemtuzumab (Anti-CD52)	Immuno-suppressive Immune reconstitution	Monoclonal antibodies	High/ Very high	IV, SC	CBC, LFT, U&E, TFT, screening for underlying infections (TB, HIV, JCV, Hepatitis B and C)	Malignancy, Hepatitis B reactivation, tuberculosis, hypersensitivity reactions, autoimmune conditions (thyroid, immune thrombo cytopenic purpura [ITP])	PPMS, RRMS, CIS, SPMS

Source: From McGinley, et al. and Dobson, et al.[8, 9]

Table 3: Prognostic Consideration in MS

Favorable factors	Unfavorable factors
• Female • Relapsing-remitting onset • Sensory symptoms or optic neuritis only • Younger age (<30) at onset • Low number of relapses early in disease course (<2 in first two years) • Complete recovery of neurological function following relapse • Long time (>5 years) until assignment of an EDSS score of 4 • Low rate of increase in lesion load on MRIs	• Male • Progressive onset • Motor symptoms, cerebellar symptoms, or bowel/bladder problems • Older age (>30) at onset • High number of relapses early in disease course (>2 in first two years) • Incomplete recovery of neurological function following relapse • Short time (<5 years) until assignment of EDSS score of 4 • High rate of increase in lesion load on MRIs, particularly in first five years after MS diagnosis

How Long Should Treatment Continue?

Once started, treatment is usually lifelong. Breakthrough disease (relapses, attacks) or adverse side effects might necessitate a change in medication. The question regarding duration of treatment, however, can become particularly challenging to answer if treatment is started at the CIS or RIS stage.

Regular neurologic examinations and MRIs are necessary, including individualized laboratory investigations based on concomitant DMT or other therapy, to keep track of the course and speed of the disease.

Trials are ongoing to evaluate whether treatment can be discontinued in patients with nonactive disease. Observational studies have suggested that a group who might benefit from a discontinuation of treatment, as they have a low risk of disease recurrence, are older individuals who have been stable clinically and radiographically for at least four years.

What Are the Prognostic Indicators?

The most important factors indicating poor prognosis for MS seem to be the number and type of attacks, presence of highly active disease, more extensive disease burden detected on imaging, and poor or partial recovery between relapses.[10]

High frequency of relapses in the first few years is a bad prognostic sign, as the average relapse rate in first few years is approximately one per year. In terms of type of attack, vision loss as a presenting symptom is associated with a better outlook whereas primary bulbar symptoms, motor attacks, or ataxia are associated with a poorer prognosis. Additional clinical factors associated with a worse prognosis are male gender, older age of onset, multifocal presentation, cognitive impairment, and involvement of pyramidal and cerebellar symptoms. These are represented in Table 3.

Conclusion

Medical science's understanding of MS continues to advance, particularly with respect to improvements in its diagnosis and treatment. Earlier diagnosis and improved imaging and other investigative tools are likely to impact disease outcomes positively.

In terms of emerging treatments, hematopoietic and mesenchymal stem cell therapy as well as remyelination therapies are being studied in ongoing clinical trials but are not yet part of standard medical care. The impact of a breakthrough treatment that could repair or reverse the significant and debilitating progression of the disease would be tremendous. The cost implications of these advances would need to be considered and balanced with the benefit of being able to restore function and reduce progressive disease and disability. Nevertheless, it is an exciting time in the evolution of the understanding and management of MS. This will be an area to continue to observe very closely for any improvements that might meaningfully impact risk assessment. RF

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