Consensus recommendations on multiple sclerosis management in Australia and New Zealand: part 1

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Abstract

Introduction: Multiple sclerosis (MS) is a chronic inflammatory demyelinating and degenerative disease of the central nervous system. There were 33 335 people with MS in Australia in 2021 and 2917 in New Zealand in 2006 and the prevalence and incidence are increasing with time. Although new treatments have substantially improved outcomes in recent decades, the treatment landscape has become increasingly complex due to the expanding number of disease-modifying therapies (DMTs) and associated safety considerations.

Main recommendations: A total of 80 consensus recommendations were developed on the current best-practice management of MS in Australia and New Zealand. Part 1 of these guidelines outlines the consensus recommendations covering domains including DMT counselling and selection, pre-DMT assessments, monitoring disease activity on DMT, switching DMT, and discontinuing DMT. The remaining recommendations are outlined in Part 2, encompassing risk mitigation strategies during treatment with DMT, managing DMT in special situations (including pregnancy, postpartum, breastfeeding, active infection including COVID-19, and malignancy), general lifestyle measures, acute MS relapses, and symptomatic treatments for MS.

Changes in management as a result of the guidelines: This two-part position statement provides a practical resource for clinicians on current best-practice consensus recommendations for managing adults (≥ 18 years old) with MS in the Australian and New Zealand health care settings. It outlines the 14 DMTs currently available through the Australian Pharmaceutical Benefits Scheme and eight through the New Zealand Pharmaceutical Schedule, including the unique efficacy, safety and monitoring considerations of each. Through these guidelines, we aim to support safe, timely and effective management of patients with MS in Australia and New Zealand.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and degenerative disease of the central nervous system (CNS) characterised by multifocal brain and spinal cord lesions. It is most commonly diagnosed in people of working age (~20–50 years) and is the leading cause of non-traumatic chronic neurological disability in young adults in many high income countries.[1] There were 33 335 people living with MS in Australia in 2021, and 2917 in New Zealand in 2006, and the prevalence and incidence are increasing with time.[1,2] Factors contributing to this trend include improved diagnosis, improved registry data, improved life expectancy of people with MS, and potentially increased exposure to risk factors for MS such as adolescent obesity, smoking, reduced sun exposure, and reduced parity.[1,3,4]

MS is diagnosed by integrating clinical, imaging, and laboratory features using the 2017 revised McDonald criteria.[5] This requires a history of two or more attacks in distinct locations in the CNS, "dissemination in space and time", supported by magnetic resonance imaging (MRI) and, in some instances, cerebrospinal fluid (CSF) findings consistent with the diagnosis and no better explanation. In patients with a first clinical episode suggestive of MS, MRI gadolinium-enhancing and non-enhancing T2 hyperintense lesions and/or CSF-restricted oligoclonal bands can be substituted as markers of dissemination in time. Dissemination in space is fulfilled on MRI scan with T2 hyperintense lesions in two or more of four regions in the CNS, including periventricular, cortical/juxtacortical, infratentorial, and spinal cord.[5] The McDonald criteria are due to be updated later in 2024.

Appropriate and conservative use of diagnostic criteria is important to avoid harm caused by misdiagnosis of MS, including potential harm from unnecessary exposure to immunotherapy. Frequent reasons for misdiagnosis include misinterpretation of non-specific neurological symptoms and misinterpretation of non-specific abnormalities detected on MRI.[6] Other CNS inflammatory disorders with distinct underlying pathologies may also be mistaken for MS and will require different management strategies. When MS is suspected, early referral to a neurologist is recommended for evaluation of MS and exclusion of alternative diagnoses. When the diagnosis remains uncertain after initial review, neurologists should consider referral to an MS specialist.

MS can present with a clinically isolated syndrome (CIS), defined as a symptomatic episode typical for MS not yet meeting the criteria for dissemination in space and time. About 60–80% of patients with CIS with MRI lesions suggestive of demyelination

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develop clinically definite MS long term.[7] Another possible precursor of MS is radiologically isolated syndrome (RIS), defined by incidental MRI lesions typical of CNS demyelination without clinical features of MS. About 30% of patients with RIS develop a clinical event and are diagnosed with MS within five years.[8]

The most frequent form of MS at onset, affecting 85% of people with MS, is relapsing–remitting MS (RRMS), traditionally characterised by discrete clinical relapses with remission and apparent stability between relapses. In some patients with an initial relapsing–remitting course, the disease later becomes progressive, with inexorable accumulation of disability with or without relapses, known as secondary progressive MS. In about 5–15%, the disease demonstrates progressive neurologic deterioration from onset and is termed primary progressive MS.[9] However, although these historical phenotypic distinctions are used in clinical trials and treatment guidelines, there is a contemporary shift to understanding MS as a single disease continuum with concurrent relapsing (inflammatory) and progressive (degenerative) biological processes.[10] In RRMS, accumulation of disability not only occurs due to relapse-associated worsening, but also progressive pathology with progression independent of relapse activity.[11] Similarly, progressive phenotypes involve both active inflammation and neurodegeneration with contribution from reduced reparative mechanisms.[10]

Disease-modifying therapy (DMT) for MS consists of immunomodulatory or immunosuppressive treatments that reduce immune-mediated inflammation in the periphery and/or CNS. The number of DMTs available for the treatment of MS has significantly increased in recent decades. In 1996, interferon (IFN)-β-1b became commercially available in Australia as the only DMT for RRMS. In 2023, there are 14 DMTs listed on the Australian Pharmaceutical Benefits Scheme (PBS) and eight on the New Zealand Pharmaceutical Schedule (Pharmac), predominantly for RRMS. Few DMTs have demonstrated efficacy in the progressive MS phenotypes.

Although the treatments for MS are not curative, there have been significant improvements in ameliorating disease activity and disability progression with the development and availability of effective DMTs.[12,13] The aim of MS treatment is to achieve no evidence of disease activity (NEDA), defined as no clinical relapses, no increase in disability, and no new lesions on MRI scan.[14] Emerging measures of monitoring MS activity such as brain volume loss and serum neurofilament light chain are not yet available everywhere, but are likely to become part of routine clinical practice in the near future.[15] Importantly, the aims of treatment are balanced with mitigating the risks associated with each DMT.

Although international guidelines have been published, up-to-date national guidelines outlining locally available therapies, government subsidies, and local practice are needed. Together with Part 2,[16] the aim of this position statement is to provide a practical resource for clinicians (general practitioners, general physicians and general neurologists) on current best-practice consensus recommendations for managing adults (≥ 18 years old) with MS in the Australian and New Zealand health care settings.

Methods

The need for clinical practice guidelines on the management of MS in Australia and Zealand was identified by the MS group of the Australian and New Zealand Association of Neurologists (ANZAN) during the 2022 and 2023 meetings. The guidelines were developed through an iterative modified Delphi consensus process between May 2023 and March 2024 guided by the principles of the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.[17,18] Participants included two Delphi Chairs (MM, JS) and a Delphi Panel comprising 34 MS neurologists with subspecialty practice in MS and neuroimmunology in Australia (n = 31) and New Zealand (n = 3).[18] Recommendations were also reviewed by a Reviewing Panel of other multidisciplinary stakeholders including MS consumers (n = 2), MS nurses (n = 2), allied health clinicians (n = 2) including a physiotherapist and psychologist with experience in MS, the MS national support group MS Plus, an infectious diseases physician, an immunologist, and a general practitioner. All conflicts of interest of contributors were disclosed. No pharmaceutical companies were involved at any stage of the formulation of these recommendations, no authors received any financial support for the development of these guidelines, and no authors stand to gain financial benefit from the implementation of the recommendations.

The scope of the guidelines was defined with representatives of the ANZAN MS group and draft recommendations were formulated by the Delphi Chairs through a review of published literature available in English at the time of writing. Prioritised literature included systematic reviews and meta-analyses, randomised-controlled trials, and, where lacking, observational studies. In addition, national medication authority guidelines and manufacturers' product information guides were reviewed for all subsidised DMTs in Australia and New Zealand. In round 1, draft recommendations were reviewed by the Delphi Panel through free-text responses (n = 32) and an anonymised multiple-choice survey with a five-point Likert scale (1, strongly disagree; 2, disagree; 3, neutral; 4, agree; 5, strongly agree) to assess initial level of agreement (n = 26). Consensus was defined a priori as agreement (agree or strongly agree) of at least 80% of panellists. All panellists were equal voting members. In round 2, new and revised recommendations were reviewed by the Delphi Panel in a second anonymised multiple-choice survey (n = 27). In round 3, remaining non-consensus recommendations were discussed in an online meeting and revised recommendations reviewed with a third survey (n = 18). Free-text feedback was also sought from the Reviewing Panel in each reviewing stage.

Recommendations were graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. The quality of the supporting evidence was defined as high (A), moderate (B), or low (C) and the strength of the recommendations was classified as strong (1) or conditional (2).[19] Where specific evidence is lacking and recommendations are based on best-practice standard of care, consensus recommendations were designated as good practice points (GPPs).

Recommendations

Consensus was reached on 80 recommendations. The results of the Delphi rounds and final consensus recommendations including level of consensus and GRADE classification are included in the Supporting Information (tables 1–3).

The Supporting Information (table 4) summarises the 14 DMTs listed on the Australian PBS and eight on the New Zealand Pharmac at the time of this publication. The DMTs are broadly

categorised as immunosuppressive (ocrelizumab, ofatumumab, sphingosine-1-phosphate [S1P] receptor modulators, fumarates, and teriflunomide), immunomodulatory (natalizumab, interferons, and glatiramer acetate), and short course immune reconstitution therapies that are transiently immunosuppressive followed by long term immunomodulation (alemtuzumab, cladribine, and autologous haematopoietic stem cell transplant [aHSCT]).[20]

Disease-modifying therapy counselling and selection

Disease-modifying therapy counselling

Before commencing a DMT, patients should be counselled about the nature of the disease, what to expect, and the implications for day-to-day life and for life choices such as pregnancy. Patients should also be counselled about the aims of DMT, the DMTs available, the associated risks and benefits, the importance of early treatment, and modifiable risk factors for disease progression (Supporting Information, table 4, and "General lifestyle measures" in Part 2 of these guidelines[16]) (*Recommendation [R]1*). Where available, a second consultation with an MS nurse specialist should also occur to further discuss DMTs and mode of administration and to address any further questions (*R2*).

DMTs for MS should be initiated and supervised by a neurologist and selection individualised to the person with MS. The choice of DMT is determined by considerations including disease phenotype, disease activity, drug efficacy, drug risk profile, John Cunningham virus (JCV) antibody status, comorbid conditions, pregnancy considerations, local accessibility, route of administration, and patients' personal preferences, values and goals (Box 1) (*R3*).

1 Patient testament

"From a patient perspective, it's actually really hard to weigh up the pros and cons of different treatments. It's one decision to be on treatment, another to work out which treatment to go on … Also with mode of administration, to talk through the burden of these and be realistic on what adherence looks like."

Relapsing–remitting multiple sclerosis

In RRMS, it is recommended that DMT is started as early as possible after diagnosis to limit irreversible disease progression.[21,22] The *International consensus on quality standards for brain health-focused care in multiple sclerosis* suggests the process of discussing and commencing DMT should be complete within three months ("core") — with about five weeks being "achievable" and 17 days being "aspirational" (*R4*).[23]

In Australia and New Zealand, high efficacy therapy (particularly natalizumab, ocrelizumab, ofatumumab or cladribine) is generally favoured as first line DMT in people with RRMS (*R5*). Early high efficacy therapy is associated with lower disability progression compared with low or intermediate efficacy therapy or commencement of high efficacy therapy non-first line.[22,24,25] The presence of risk factors predictive of a poor prognosis strongly favours first line high efficacy therapy (particularly infusional therapy), such as infratentorial and/or spinal cord lesions, a short duration between first and second relapse, and early disability accrual.[26] However, following an informed discussion between the patient and the consultant, there are circumstances where intermediate or low efficacy therapy is indicated (*R6*).

Progressive multiple sclerosis

The evidence of effectiveness of DMTs in progressive MS is limited. Therefore, when considering therapy for progressive MS, the risk of adverse effects needs to be carefully weighed against the likelihood of slowing disease progression (*R7*).

In secondary progressive MS, siponimod has been shown to reduce the risk of disability progression. In the EXPAND trial, siponimod was associated with a relative risk reduction in the proportion of patients with three-month confirmed disability progression of 21% compared with placebo. Though not powered for subgroup analysis, the study suggested the effect on confirmed disability progression was more pronounced in patients with recent disease activity (superimposed relapses in the two years preceding enrolment) and rapid progression. The effect appeared less pronounced with older age, increased disability, and longer duration of MS.[27] Siponimod is available on the Australian PBS for some patients with secondary progressive MS (those who are ambulatory with/without assistance and without continuing progression of disability on siponimod),[28] but not yet on the Pharmac in New Zealand.

In ambulatory patients with progressive MS, ocrelizumab has shown benefit in reducing clinical and radiological disease progression. In the ORATORIO trial, there was a relative risk reduction of 24% in the proportion of patients with three-month confirmed disability progression with ocrelizumab compared with placebo.[29] Ocrelizumab is not currently subsidised for progressive MS in Australia, but it is registered with the Therapeutic Goods Administration (TGA) for use in progressive MS.[30] In New Zealand, ocrelizumab has been subsidised for progressive MS since 1 September 2023.[31]

Clinically isolated syndrome

In individuals with CIS meeting the criteria for dissemination in space on MRI scan but not fulfilling the criteria for dissemination in time, lumbar puncture for intrathecally restricted oligoclonal bands can be offered as a probabilistic substitute for dissemination in time. This allows the diagnosis of MS and treatment according to the recommendations for RRMS (refer to the "Relapsing–remitting multiple sclerosis" section above) (*R8*).[5,32,33]

Glatiramer acetate, IFN-β and teriflunomide have demonstrated efficacy in reducing the risk of clinically definite MS in individuals with CIS and at least two T2 lesions.[34-38] Although there are currently no subsidised DMTs for CIS in Australia or New Zealand, glatiramer acetate and IFN-β are registered with the Australian TGA and New Zealand Medicines and Medical Devices Safety Authority (Medsafe) for use in CIS with at least two clinically silent lesions characteristic of MS on MRI scan.[38-41] Individuals with a first demyelinating event with MRI showing abnormalities typical of MS should be considered for DMT, especially those with intrathecally restricted oligoclonal bands (*R9*).

Radiologically isolated syndrome

In general, people with RIS should be monitored for the development of clinical manifestations and new demyelinating lesions on MRI scan at least annually for at least five years (*R10*). Factors associated with conversion from RIS to CIS or clinically definite MS include younger age, male sex, cervical or thoracic spinal cord lesions, and CSF-restricted oligoclonal bands.[8,42]

2 Pre-immunotherapy screen

Tests

- Hepatitis B serology (HbsAg, anti-HbsAb, anti-HbcAb)
- Hepatitis C serology
- HIV serology
- Syphilis serology
- Latent *Mycobacterium tuberculosis* testing (interferon-γ release assay [QuantiFERON-TB Gold] with/without chest x-ray)
- VZV serology (IgG)
- Measles, mumps and rubella serology (IgG), particularly in women considering future pregnancy
- *Strongyloides* serology (IgG)
- JCV serology (IgG) if natalizumab is being considered (see "Progressive multifocal leukoencephalopathy" in Part 2[16])*

Anti-HbcAb = anti-hepatitis B core antibody; anti-HbsAb = anti-hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; JCV = John Cunningham virus; VZV = varicella zoster virus. * Requires collection in a Unilabs Stratify JCV Testing Pack which is sent to Unilabs (Denmark). ◆

The benefit of treating RIS with DMT is currently under investigation. Recent studies have demonstrated dimethyl fumarate and teriflunomide significantly extended the time to a first clinical demyelinating event in people with RIS.[43,44] There are currently no registered or subsidised DMTs for RIS in Australia or New Zealand. Advice from MS specialist neurologists should be sought in treatment decisions in radiologically isolated MS (*R11*).

Evaluation before commencing disease-modifying therapy

Pre-immunotherapy screen

Before commencing DMT, perform a pre-immunotherapy screen to identify active and latent infections at risk of worsening with immunotherapy and to assess immunisation status (Box 2) (*R12*). If an important active or latent infection is identified, the patient should be referred to an appropriate specialist (eg, infectious diseases physician or hepatologist) for assessment and treatment before initiation of DMT (*R13*). Of note, patients with serological evidence of chronic active hepatitis B infection (hepatitis B surface antigen [HbsAg] positive, hepatitis B virus DNA positive) or evidence of prior exposure (anti-hepatitis B core antibody [anti-HbcAb] positive, HbsAg negative) should be referred to an infectious diseases physician or hepatologist before DMT commencement. The specialist will consider antiviral therapy (eg, entecavir) for patients with chronic infection and consider antiviral therapy or surveillance for those with evidence of prior exposure to minimise the risk of reactivation (*R14*). Patients receiving anti-CD20 therapy are at highest risk of hepatitis B reactivation and anti-CD20 therapy is contraindicated without prophylaxis. Prophylaxis should continue for up to 18–24 months after cessation of anti-CD20 monoclonal antibodies (*R15*).[45]

Immunisations

Review the patient's immunisation history and aim to ensure that they are up to date with the Australian National Immunisation Program Schedule or New Zealand National Immunisation Schedule, as relevant (refer to Box 3 for recommended vaccines in people with MS).[58,59] Particular attention should be paid to varicella zoster and hepatitis B vaccinations. However, delaying DMT to complete vaccinations may not be feasible in all cases, especially in the setting of highly active MS (*R16*).

All indicated live and live-attenuated vaccinations should be given at least four to six weeks before starting certain immunosuppressant DMT (eg, anti-CD20 monoclonal antibodies) to ensure the vaccines are safe and effective (*R17*). To allow time for a vaccine response, non-live vaccines should be completed two to six weeks before some DMTs (alemtuzumab, anti-CD20 therapies), as per TGA guidelines (Supporting Information, table 4) (*R18*).

Baseline laboratory tests and examination

Perform baseline laboratory tests relevant to the particular DMT (eg, full blood examination, creatinine, liver function tests, quantitative serum immunoglobulins, pregnancy test, urinalysis, electrocardiogram, optical coherence tomography, cervical smear) and relevant examinations (eg, skin, ophthalmic) (Supporting Information, table 4). These tests are not required before all therapies (*R19*).

Monitoring disease activity on disease-modifying therapy

Monitor people with MS receiving DMT for symptoms and/or signs of disease activity, including acute clinical relapses and progression of disability (*R20*). Disability is measured and monitored over time with the Expanded Disability Status Scale (EDSS), which is a scale from 0 to 10, with higher numbers indicating more severe impairment.[60]

Obtain a re-baselining MRI scan of the brain and/or spine within three to six months of treatment commencement (*R21*). New lesions may develop before the DMT reaches full efficacy. If there are new lesions on the re-baselining scan, arrange an interval MRI scan in three to six months to ensure radiological disease stability (*R22*). In patients with long term disease stability and low risk of progressive multifocal leukoencephalopathy, interval MRI scan is generally performed every 12 months (see "Progressive multifocal leukoencephalopathy" in Part 2[16]). In patients with active disease or moderate to high risk of progressive multifocal leukoencephalopathy, MRI scan is generally performed every three to six months (*R23*). Interval imaging is often limited to a non-contrast MRI scan of the brain annually and MRI scan of the spine annually to bi-annually depending on new spinal cord symptoms.

Switching disease-modifying therapy

Indications for switching disease-modifying therapy

Switching to another DMT is recommended if there is evidence of breakthrough clinical disease activity (one or more clinical relapses) or radiological disease activity (one or more new T2 hyperintense lesions) after being on and adherent to a DMT for a sufficient time for it to be fully effective (*R24*).[61] In older patients and those with other comorbid conditions (eg, migraine), lesions can arise for other reasons; therefore, it is important to assess that the location of a new lesion is consistent with central demyelination.

Switching DMT should also be considered if the risk of continuing outweighs the benefit or serious or intolerable adverse effects occur (*R25*). If pregnancy is being considered, see "Pregnancy" in Part 2.[16]

Sequential disease-modifying therapy selection and washout period

In addition to considerations outlined in the section "Disease-modifying therapy counselling and selection", choice of sequential DMT is determined by considerations such as

3 Vaccinations in people with multiple sclerosis

Vaccine	Live/non-live	Recommended population	Schedule	Considerations
Varicella zoster (chickenpox)	Live-attenuated	• Lack of serological immunity and no history of chickenpox, shingles or vaccination[46]	• 2 doses at least 4 weeks apart before commencing DMT[46]	• Serological testing is not required after vaccination[47] • When DMT cannot be delayed, do not vaccinate. Consider antiviral prophylaxis in high risk situations[48]
Herpes zoster (shingles)	Non-live (Shingrix; GSK)	• Adults ≥ 18 years old who are or soon to be immunocompromised • Not required if previous varicella zoster vaccine and no history of subsequent varicella infection • Immunocompromised individuals can receive the vaccine from 3 months after an episode of herpes zoster (shingles)[49]	• 2 doses 1–2 months apart in immunocompromised individuals, ideally before commencing DMT[49]	• The live zoster vaccine (Zostavax; Merck) is not recommended now Shingrix is available[49] • Shingrix is recommended for all immunocompromised patients as per the Australian Immunisation Handbook,[49] but of note currently, a 2-dose course of Shingrix is only available for free for: ▸ people aged ≥ 65 years; ▸ First Nations people aged ≥ 50 years; ▸ immunocompromised people aged ≥ 18 years with the following medical conditions: haematopoietic stem cell transplant, solid organ transplant, haematological malignancy, or advanced or untreated HIV;[50] ▸ in New Zealand, free for 1 year after turning 65 years old[51]
Hepatitis B	Non-live	• Lack of serological immunity, particularly if occupational or lifestyle risk factors for hepatitis B infection (eg, health care workers, tattoos)[52]	• Standard 3-dose schedule is vaccines at 0, 1 month, and 6 months — 0, 1, 4 months and 0, 2, 4 months are also acceptable[52]	• Serological testing is recommended 4–8 weeks after completing the vaccination course. If anti-HbsAb < 10 mIU/mL (non-responder), a booster dose and repeat serological testing is recommended. Seek specialist advice[52]
Human papillomavirus	Non-live	• Non-vaccinated adolescents and adults who are or soon to be immunocompromised, including with significant immunosuppressive therapy[53]	• 3 doses of 9vHPV vaccine at 0, 2 and 6 months[53]	
Measles, mumps, rubella	Live	• Lack of serological immunity and no documented evidence of vaccination,[54] especially in women considering future pregnancy	• 2 doses at least 4 weeks apart before commencing DMT[54]	
Diphtheria–tetanus–pertussis	Non-live (dTpa)	• Primary: lack of serological immunity and no history of dT vaccine • Booster: last vaccine or booster > 10 years ago[55]	• Primary: 3 vaccines at least 4 weeks apart (dTpa, dT, dT) • Booster: dTpa[55]	
Influenza	Non-live	• All people with MS	• Annually	
COVID-19	Non-live	• All people with MS	• Full course of COVID-19 vaccinations as per the ATAGI recommendations including booster doses[56]	• Review the latest recommendations of the relevant national advisory body

Continues

3 Continued

Vaccine	Live/non-live	Recommended population	Schedule	Considerations
Pneumococcus	Non-live	• Adolescents or adults who are or soon to be immunocompromised[57]	• 1 dose of 13vPCV, 15vPCV or 20vPCV; and • 1 dose of 23vPPV 2–12 months later; and • A second dose of 23vPPV at least 5 years after the first dose of 23vPPV[57]	• Currently 13vPCV and 23vPPV are funded under the Australian NIPS for eligible individuals, but this is likely to change. Consult the Australian Immunisation Handbook for up-to-date recommendations[57]

9vHPV = 9-valent human papillomavirus vaccine; 13vPCV = 13-valent pneumococcal conjugate vaccine; 15vPCV = 15-valent pneumococcal conjugate vaccine; 20vPCV: 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; anti-HbsAb = anti-hepatitis B surface antibody; ATAGI = Australian Technical Advisory Group on Immunisation; dT = diphtheria-toxoid vaccine; dTpa = diphtheria, tetanus and pertussis vaccine; HPV = human papillomavirus; NIPS = National Immunisation Program Schedule. Note: Refer to the Australian (https://www.health.gov.au/resources/publications/the-australian-immunisation-handbook?language=en) or New Zealand Immunisation Handbook (https://www.tewhatuora.govt.nz/for-health-professionals/clinical-guidance/immunisation-handbook) for patients at risk of other infections (eg, meningococcal disease, Mpox) and travel vaccine information. Seek expert advice if these vaccinations are required. ◆

implications of previous immunosuppressive therapies and comparative drug efficacy (*R26*).

There is limited evidence to guide the optimal duration of washout periods; refer to the Supporting Information (table 4) for a general guide. However, the individualised risk–benefit balance should be carefully considered when determining the duration off DMT. Notably, lymphocyte antitrafficking therapies natalizumab and fingolimod are associated with a risk of rebound disease activity after discontinuation.[62-64] Rebound disease activity generally refers to a severe clinical relapse, increased disability beyond pre-treatment levels, and/or new demyelinating lesions on MRI (gadolinium-enhancing or tumour-like demyelinating lesions). A washout period of more than four to eight weeks should therefore be avoided for natalizumab and S1P receptor modulators (*R27*).

Autologous haematopoietic stem cell transplant

aHSCT involves collection of an individual's own stem cells, administration of conditioning chemotherapy, and re-infusion of the stem cells to reconstitute the immune system. Through restoring immune function, aHSCT can be a highly effective treatment for MS in specific circumstances. A meta-analysis of 15 studies on aHSCT in people with MS with severe treatment-resistant disease showed a pooled NEDA of 83% at two years and 67% at five years. The greatest benefit was seen in people with highly active inflammatory RRMS without high levels of disability.[65] A recent retrospective observational study comparing aHSCT with fingolimod, natalizumab and ocrelizumab demonstrated aHSCT was substantially superior to fingolimod and marginally superior to natalizumab over five years. There was no statistically significant difference between aHSCT and ocrelizumab over the shorter available follow-up period of three years.[66] However, as a result of the profound impact on the immune system, risks include infection, secondary autoimmune disease, secondary malignancy, endocrine abnormalities, infertility, cardiovascular disease and, rarely, death.

aHSCT is used in a small number of carefully selected patients with severe refractory active RRMS without high levels of disability. It is generally reserved for younger adults (< 65 years old) with lower baseline disability (EDSS ≤ 6.5) who have failed two or more high efficacy DMTs due to continued clinical and radiological disease activity. Neurologists can consider referring appropriate patients with MS for assessment by an MS neurologist in a major tertiary centre with experience in aHSCT for MS where cases are reviewed by the national aHSCT committee and their follow-up trajectory monitored as per national standards. Appropriate people with MS in New Zealand can be referred for review by the aHSCT committee of Australia (*R28*).

Discontinuing disease-modifying therapy

There are insufficient data regarding the risk–benefit of discontinuing ongoing DMT.[67] In studies of people with RRMS, discontinuing DMT was associated with an increased risk of relapse, disability progression, and radiological disease activity.[68,69] Predictors of relapse after DMT discontinuation include younger age, female sex, higher EDSS, and higher relapse activity in the 12 months before discontinuation.[64,70] In general, it is recommended that patients with RRMS continue DMT if they are clinically stable and not experiencing significant adverse effects. For patients of older age (> 65 years) and at greater risk of side effects, careful consideration should be given to DMT cessation or de-escalation (*R29*). For patients who decide to discontinue DMT, close clinical and radiological monitoring is recommended (*R30*). In patients with progressive MS, consider discontinuing DMT if the risks outweigh the benefits or there is significant disability progression (EDSS ≥ 7) (*R31*). Discontinuation trials are ongoing and current data on discontinuation are lacking. Research investigating the risk–benefit considerations related to DMT use in older patients is also ongoing, including on the effect of ageing-related immunosenescence on MS activity.

Limitations

Due to the comprehensive scope of the entire set of recommendations, a systematic review of all available literature on each domain of MS management was not performed (see the "Methods" section for prioritised literature). GRADE Evidence to Decision tables were not used; a pragmatic approach to GRADE assignment was adopted considering pivotal literature and other relevant considerations outlined in the Supporting Information (table 1).

Conclusion

MS is a chronic neuroinflammatory disease with a rapidly evolving treatment landscape. At present, 14 DMTs are listed on the Australian PBS and eight on the New Zealand Pharmac with unique efficacy, safety and monitoring considerations.

The recommendations in this consensus statement are based on current evidence-based literature and Delphi-derived consensus of a specialist group working in MS in Australia and New Zealand. Updated guidelines will be required when treatment options change and further long term safety data become available. Importantly, MS is a heterogenous disease and individualised clinical assessment and application of the guidelines are essential.

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Simon Broadley has received honoraria for attendance at advisory boards, speaker fees and sponsorship to attend scientific meetings from Novartis, Biogen-Idec, Sanofi–Genzyme, Roche, Bayer–Schering, Teva, CSL, and Merck Serono, and has been a principal investigator for clinical trials sponsored by Biogen–Idec, Novartis, Sanofi–Genzyme, and ATARA. Helmut Butzkueven is an employee of Monash University and has accepted travel compensation from Merck; his institution receives honoraria for talks, steering committee activities, and research grants from Roche, Merck, Biogen, Novartis, and UCB Pharma, Medical Research Future Fund Australia, NHMRC Australia, Trish MS Foundation, MS Australia and the Pennycook Foundation. He receives personal compensation for steering group activities for the Brain Health Initiative from Oxford Health Policy Forum and is funded by an NHMRC Australia Investigator Grant (GNT1197339). Katherine Buzzard is principal investigator in clinical trials for Novartis, Merck, Roche and Biogen. She has received speaker honoraria and/or travel grants from Sanofi–Genzyme, Roche, Alexion, Merck, Biogen, Novartis and Teva. She has been on advisory boards for Merck, Biogen and UCB. Yi Chao Foong has received funding support from the NHMRC, Australia and New Zealand Association of Neurologists, AVANT foundation and MS Research Australia. He has received travel compensation from Biogen and Novartis. Lauren Giles has served on advisory board for Teva. Todd Hardy has received honoraria for talks, advisory boards or support for scientific meetings from Bayer–Schering, Novartis, Biogen Idec, Merck, Teva, Merck, Alexion, Bristol Myers Squibb and Sanofi–Genzyme. He has been the principal investigator on the phase 4 trials in MS funded by Novartis and Sanofi–Genzyme. 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Supporting Information

Additional Supporting Information is included with the online version of this article.