Consensus recommendations on multiple sclerosis management in Australia and New Zealand: part 2

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Abstract

Introduction: Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system with rapidly evolving treatment options and strategies. An iterative modified Delphi process was used to develop 80 consensus recommendations for the management of MS in Australia and New Zealand. Part 1 of these guidelines includes recommendations related to selection of initial disease-modifying therapy (DMT) for MS, assessments before commencing DMT, monitoring disease activity on DMT, switching DMT, and discontinuing DMT.

Main recommendations: This article, Part 2, covers recommendations related to risk mitigation during treatment with DMT, managing DMT in special situations (including pregnancy, postpartum, breastfeeding, active infection including COVID-19, and malignancy), general lifestyle measures for MS, acute MS relapses, and symptomatic treatments.

Changes in management as a result of the guidelines: Together with Part 1, this consensus statement provides practical guidance for clinicians involved in the care of adults (≥ 18 years old) with MS in Australia and New Zealand. A safe, effective and comprehensive approach to managing MS is crucial for improving long term outcomes and quality of life in individuals affected by MS.

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) with rapidly evolving treatment options and strategies. The need for these guidelines was identified by the MS Interest Group of the Australian and New Zealand Association of Neurologists (ANZAN). Please refer to Part 1 for a detailed background to this article and the iterative modified Delphi process used to develop the consensus recommendations.[1] The full list of recommendations is included in the Supporting Information (table 1), including the level of consensus for each recommendation and the classification using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.

Please also refer to the Supporting Information (table 4) in Part 1 for a comprehensive summary of the 14 disease-modifying therapies (DMTs) currently listed on the Australian Pharmaceutical Benefits Scheme (PBS) and eight on the New Zealand Pharmaceutical Schedule (Pharmac) at the time of this publication.[1]

Recommendations

Risk mitigation strategies during treatment with disease-modifying therapies

MS DMTs have associated risks, as highlighted in the Supporting Information (table 4) of Part 1;[1] however, the risks are generally lower than the risk of untreated relapsing–remitting MS, particularly if the following risk mitigation strategies are implemented.

Laboratory monitoring

Monitor relevant laboratory tests in patients receiving DMT, as summarised in the Supporting Information (table 4) in Part 1.[1] Switching DMT might be warranted if significant or serious abnormalities occur (*Recommendation [R] 32*).

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare and often fatal opportunistic infection of the CNS caused by John Cunningham virus (JCV) reactivation in individuals with impaired cellular immunity or inhibited CNS immune surveillance. It primarily occurs in patients with human immunodeficiency virus infection, haematological malignancy, or MS receiving natalizumab. Rare cases of PML have also been reported in people with MS receiving dimethyl fumarate, fingolimod, ozanimod, alemtuzumab and ocrelizumab.[2-6] PML presents with progressive multifocal neurological deficits, such as weakness, sensory change, ataxia, cortical vision impairment, aphasia, cognitive dysfunction, and/or behavioural change. Seizures are also common.[7] Changes on magnetic resonance imaging (MRI) scans of the brain typically include multifocal asymmetric confluent T2 FLAIR (T2-weighted fluid-attenuated inversion recovery) hyperintensities. In natalizumab-related PML, multiple punctate T2 hyperintense lesions are often seen at the border of the PML lesion ("Milky Way sign").[8]

Before commencing natalizumab therapy and during treatment, the risk–benefit balance of natalizumab (specifically the risk of PML) should be discussed (*R33*). The risk of PML in

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people with MS on natalizumab is increased with anti-JCV antibody positivity (especially with an antibody index >0.9), treatment duration (especially more than two years), and prior immunosuppressant exposure (eg, mitoxantrone, methotrexate, azathioprine, cyclophosphamide or mycophenolate).[9-11] The risk is lowest in anti-JCV antibody negative patients with an annualised risk of less than one in 10 000 developing PML. The annualised risk in anti-JCV antibody positive patients with a treatment duration of more than two years (25–48 months) and prior immunosuppressant exposure is about one in 100.[9] To aid in quantifying the risk of PML on natalizumab, perform anti-JCV antibody testing every six months and use established risk algorithms (Supporting Information, table 2) (*R34*).[11] Anti-JCV antibody monitoring has only been validated and quantified as a risk factor for natalizumab treatment.[10]

People with MS receiving natalizumab should be monitored for clinical and radiological evidence of PML. Therapy should be suspended immediately if there is any concern for PML and the patient should be referred to a specialist centre (*R35*). The role of plasma exchange and emerging therapies such as checkpoint inhibitors and allogeneic virus-specific T cells remains uncertain in natalizumab-related PML.[12,13] In the setting of neurological deterioration associated with immune reconstitution inflammatory syndrome (IRIS), high dose corticosteroids (often 1 g intravenous methylprednisolone for five days followed by tapering oral steroids) are recommended (*R36*).[14]

Mitigating infection risk

Infection mitigation strategies are important in reducing the risk associated with immunosuppressive DMTs. While on therapy, it is recommended that all people with MS are up to date with the relevant national immunisation schedule, including annual influenza vaccinations (non-live formulation) and coronavirus disease 2019 (COVID-19) vaccinations in line with national guidelines (*R37*). Vaccine response may be less effective during treatment with certain DMTs and timing in relation to DMT should be considered to optimise vaccine response. In general, live and live-attenuated vaccines should not be administered during treatment with immunosuppressive DMTs. However, there are exceptions for which infectious diseases consultation should be sought (*R38*). Refer to the Supporting Information (table 4) in Part 1 for circumstances when infection prophylaxis, such as herpes virus prophylaxis, is recommended to reduce the risk of infection.[1]

Cancer screening

Immunosuppressive DMTs may be associated with an increased risk of malignancy. However, although medication information guides warn of malignancies diagnosed during clinical trials and in a post-marketing setting, studies have not clearly demonstrated an excess incidence of malignancy in people with MS who are receiving DMTs compared with the general MS and/or wider population (Supporting Information, table 3). However, sphingosine-1-phosphate (S1P) inhibitors may confer an increased risk of cutaneous malignancy, particularly basal cell carcinoma.[15,16] Long term registries are required to adequately assess the risk of malignancy associated with DMT use.

For all people with MS receiving DMT, it is recommended that standard age-appropriate national cancer screening guidelines are followed (*R39*). However, in women receiving moderate or high efficacy therapy in whom an oncogenic human papilloma virus (HPV) type has not been detected, cervical cancer screening with an HPV test is recommended every three years (*R40*).[17,18] Skin checks are also recommended at least annually for patients receiving S1P receptor modulators (*R41*).[16]

Managing disease-modifying therapies in special situations

Pregnancy

The risk of MS relapse is reduced during pregnancy, particularly in the third trimester. However, the relative risk reduction may not be sufficient to suppress disease activity, particularly in patients with highly active disease pre-conception.[19,20] Pregnancy plans should be discussed with women of childbearing potential before commencing DMT and regularly thereafter to carefully plan the best approach to DMT selection and management (*R42*). The decision to continue or temporarily discontinue DMTs during pregnancy is individualised based on factors such as the individual's clinical and radiological disease activity and disease severity, DMT safety in pregnancy, the risk of rebound activity after DMT discontinuation, and personal preferences and values (*R43*).

DMTs associated with significant risks in pregnancy, including teriflunomide, fingolimod, siponimod and ozanimod, should not be given to pregnant women or women of childbearing age who are not using highly effective contraception (*R44*). If a woman with MS has an unplanned pregnancy while receiving one of these teratogenic DMTs, discontinue the DMT immediately and refer to an obstetrician for further assessment (*R45*). If a patient with MS becomes pregnant while receiving teriflunomide, discontinue the drug immediately, initiate an accelerated elimination procedure (eg, a cholestyramine washout or activated charcoal), and arrange a referral to an obstetrician for further assessment (*R46*).[21] Cladribine is another teratogenic DMT and should not be administered during pregnancy. Individuals can consider conception six months after completing the last course of cladribine.[21] If pregnancy occurs after the first year course of cladribine, the second year course should be delayed until after delivery and breastfeeding (*R47*).

If an individual wishes to discontinue another DMT before pregnancy, the risk–benefit considerations should be discussed. This includes the risks associated with fetal DMT exposure and the risk of MS disease activity and disability accrual with discontinuation. The Australian Therapeutic Goods Administration (TGA) pregnancy safety categories for all DMTs are listed in the Supporting Information (table 4) in Part 1.[1] While long term studies assessing the developmental risk associated with DMT use during pregnancy are lacking, an increasing number of studies are supporting the safety of certain DMTs.[21] Conversely, discontinuing DMTs before pregnancy is associated with an increased risk of maternal disease activity, including significant rebound disease.[19,22,23] Following a careful risk–benefit discussion with the patient, discontinuing DMT before pregnancy can be considered in individual circumstances taking into consideration personal preferences, recent disease activity, and DMT type (*R48*).

In individuals with highly active MS, briefly delaying pregnancy to allow disease control should generally be discussed. Pregnancy outcomes are improved in women with stable disease pre-conception and, therefore, a period of disease stability is generally preferred before pregnancy.[20,24] However, individual circumstances should always be considered (*R49*).

In people with active disease or adverse prognostic factors who wish to become pregnant, a shared decision can be made

to continue certain DMTs where the risk of disease activity outweighs the risk associated with DMT exposure during pregnancy (*R50*). An increasing number of studies are supporting the use of natalizumab up to the third trimester of pregnancy, especially in highly active disease.[19,21,25,26] A small study (n = 13 pregnancies) showed that natalizumab exposure in late pregnancy was associated with mild to moderate haematological abnormalities, including anaemia or thrombocytopaenia, in the majority of newborns.[27] However, this observation is yet to be validated. Natalizumab can be continued until the third trimester and extended interval dosing (every six weeks) up to 30–34 weeks' gestation can be considered (*R51*).[19,21]

Emerging studies are supporting the use of anti-CD20 monoclonal antibodies in the lead-up to pregnancy.[28-30] Although it was previously recommended that ocrelizumab be ceased six to twelve months before planned conception, aiming for conception three months after the last infusion can be considered (*R52*).[21,31] Of lower efficacy therapies, glatiramer acetate is considered safe in pregnancy (*R53*).[21,32]

Treatment of MS relapses during pregnancy is only recommended when symptoms are functionally disabling. A short course of non-fluorinated corticosteroids (such as methylprednisolone) is generally considered low risk after the first trimester (refer to the section "Acute multiple sclerosis relapses" for approach) (*R54*).[21] Although a small increased risk of oral clefts has been reported with antenatal exposure to corticosteroids during the first trimester,[33] this finding has been inconsistent.[34] If MRI is required, gadolinium contrast should generally be avoided due to potential risks associated with fetal exposure (*R55*).[35]

Postpartum and breastfeeding

While the risk of MS relapse is reduced during pregnancy, there is an increased risk of relapse during the first three months postpartum. Women with disease activity before and during pregnancy are at the highest risk.[19,20,36] Early resumption of DMT is generally recommended to reduce the risk of postpartum relapse.[21,22,25] Timing of DMT recommencement varies based on disease activity before and during pregnancy, risk of rebound disease activity off DMT, and safety considerations surrounding breastfeeding (*R56*). Of particular note, aim to recommence natalizumab within two weeks after birth due to the risk of rebound disease activity after natalizumab withdrawal (*R57*).[21,22]

It is well established that breastfeeding has many maternal and infant health benefits. Breastfeeding, particularly exclusive breastfeeding, may also reduce the risk of postpartum relapse in women with MS.[19,37] The benefits of breastfeeding should be discussed with women along with safety considerations related to DMTs during breastfeeding (*R58*).

The long term effects of DMT exposure on infants are not completely known. DMTs composed of large protein molecules, including glatiramer acetate, interferon-β, natalizumab, ocrelizumab and ofatumumab, may be excreted in small amounts in breast milk. However, it is likely that they are digested in the infant's gastrointestinal tract and not absorbed in significant amounts from mature breast milk (≥2 weeks postpartum).[21] Glatiramer acetate and interferon-β are considered safe during breastfeeding (*R59*).[21,38] Natalizumab is likely safe during breastfeeding, as small studies have not identified an increased risk of adverse effects in newborns exposed to natalizumab through breast milk (*R60*).[21,39] Ocrelizumab and ofatumumab are also likely safe, though there may be a very low risk of neonatal B-cell depletion, infection, and impaired vaccine response (*R61*).[21,40] In neonates with B-cell depletion from anti-CD20 therapy, live vaccines should be delayed until B-cell counts have recovered (*R62*).[21,40,41]

DMTs comprised of small molecules, including fingolimod, siponimod, ozanimod, teriflunomide and cladribine, are not considered safe in breastfeeding (*R63*). There is currently a lack of substantive evidence regarding the safety of dimethyl fumarate and diroximel fumarate during breastfeeding.[21]

Active infection

Administration of immunosuppressive DMT should be temporarily delayed if a person with MS develops a life-threatening infection or there is poor response to initial antimicrobial therapy. However, withholding therapy provides minimal short term protective benefit due to the long half-lives of many DMTs and the latency of the impact on white cell function and reconstitution. Risk of significant rebound disease activity as a result of suspending DMT (such as S1P receptor inhibitors) should also be carefully considered (*R64*). In people with MS with severe or recurrent serious infections, switching to a DMT with a lower risk of infection should be considered (*R65*).

COVID-19 infection

Immunosuppressive DMTs may increase the risk of more severe COVID-19 infection. Rituximab and ocrelizumab are associated with more severe COVID-19 infection including increased risk of hospital and intensive care unit admission.[42] Ofatumumab, another anti-CD20 therapy, may have a similar effect. However, no association has been observed between DMTs and COVID-19-associated mortality.[42] People with MS should be counselled about the importance of COVID-19 vaccinations and general behavioural modification strategies to reduce the risk of COVID-19 infection (*R66*). In people with MS who are on immunosuppressive therapies and experience acute COVID-19 infection, COVID-19-specific treatments (ie, antivirals) should be commenced promptly as per up-to-date protocols (*R67*). In the case of severe COVID-19 infection, administration of immunosuppressive DMT should generally be delayed until the infection has resolved, although the lack of acute protective benefit from delaying DMT and the risk of rebound disease activity should be considered (*R68*).

Current or previous malignancy

There are currently no guidelines on DMT use in people with MS with a current or previous malignancy.[43] When a patient has a current or past malignancy, decisions regarding DMT management are made on a case-by-case basis taking into consideration factors such as the type, recency and grade of malignancy and risk of DMT. Caution should be exercised in patients with a current or previous malignancy and specialist advice sought. People at high risk of skin cancers should avoid S1P receptor inhibitors (*R69*).[44]

General lifestyle measures

Resources such as www.msbrainhealth.org provide information on a comprehensive approach to wellness for people with MS.

Exercise

Exercise can improve cardiorespiratory fitness, functional capacity, fatigue, strength, balance, and quality of life in people with MS.[45,46] People with MS are recommended to participate in

regular exercise, including aerobic and resistance training, to a minimum weekly total of 2.5 hours (*R70*).[47] When completing aerobic training, high intensity interval training may help to mitigate the effects of heat sensitivity.[48] Furthermore, some people with MS find cooling vests helpful during periods of exercise or warmer weather.

At higher disability levels, guidance from allied health clinicians such as physiotherapists, occupational therapists, and exercise physiologists with experience in MS is recommended to develop individualised exercise programs that are safe and effective (*R71*).[47]

Diet and dietary supplements

There have been several small, heterogeneous short term studies of dietary interventions for MS.[49-53] However, due to the limitations of the presently available studies, including contradictory dietary interventions and strong treatment indication bias, there is currently insufficient evidence to support a specific dietary intervention in MS.

There is no evidence for polyunsaturated fatty acids (including omega-3 and omega-6 fatty acids) or antioxidant supplementation in MS at present.[54] A very small phase 2 trial of the antioxidant α-lipoic acid (ALA) was associated with reduced brain atrophy in secondary progressive MS, though clinical benefit was not demonstrated.[55] Despite results of a phase 2 trial showing benefit associated with high dose biotin in progressive forms of MS,[56] this was not replicated in a subsequent larger phase 3 trial.[57]

Smoking cessation

Cigarette smoking is associated with increased conversion of clinically isolated syndrome to MS, brain atrophy, disability scores, and progression of relapsing–remitting MS to secondary progressive MS.[58-60] People with MS should be strongly counselled and supported to cease and avoid smoking, including vaping (*R72*).

Vitamin D supplementation

Lower serum vitamin D is a known risk factor for MS and lower serum levels have been associated with higher radiological disease activity in patients with relapsing–remitting MS.[15,44,60] However, the recent phase 2b PrevANZ trial did not demonstrate that vitamin D supplementation delays the development of new clinical or radiological disease activity after a high risk clinically isolated syndrome,[61] nor have studies shown that vitamin D reduces relapse rate in established MS.[62,63]

There is an increased risk of osteoporosis with people with MS due to reduced mobility and chronic inflammatory disease activity.[64] Although there is no benefit in modulation of disease activity, maintaining adequate serum vitamin D levels is recommended to promote bone health through adequate safe sun exposure and vitamin D supplementation where required (*R73*).

Acute multiple sclerosis relapses

Pseudorelapses

A pseudorelapse of MS is a transient worsening of existing neurological symptoms without new CNS demyelination. Pseudorelapses can be caused by external factors such as concurrent medical illness (eg, infection), elevated body temperature (eg, fever, heat exposure, physical exertion), psychological stress, and constipation.[65] When a person with MS presents with neurological symptoms suggesting a potential relapse of MS, assess for possible precipitants such as infection that might explain the deterioration. However, differentiating relapses and pseudorelapses can be difficult. A comprehensive assessment, including a thorough history, neurological examination and, in some instances, imaging, is required for accurate differentiation (*R74*). Manage a pseudorelapse by treating the underlying cause (*R75*).

Multiple sclerosis relapses

There must be active consideration given to the presence of infection before initiating steroids for MS relapses. Steroids are contraindicated until infection is excluded. After infection or other intercurrent medical illness is excluded, acute or subacute symptomatic neurological episodes with functionally disabling symptoms lasting more than 24 hours are treated with intravenous or oral methylprednisolone 1 g for three to five days. Mild relapses, particularly those characterised by isolated sensory symptoms, generally do not warrant steroid treatment (*R76*). Short term methylprednisolone has been shown to reduce the risk of symptoms worsening within five weeks by 60% and meta-analyses have shown oral methylprednisolone 1 g daily is not inferior in efficacy to intravenous treatment.[66-68] In severe refractory relapses, a second course of methylprednisolone or plasma exchange can be considered (*R77*).[69]

Acute clinical relapses should be evaluated with MRI scan of the brain or spine with gadolinium contrast, but treatment need not be delayed for this (*R78*).

Symptomatic treatments

Common symptoms and challenges encountered by people with MS include fatigue, weakness, sensory change, spasticity, urinary urgency and retention, incontinence, heat sensitivity, speech and swallowing deficits, visual impairment, gait dysfunction, pain, depression, anxiety, and difficulty adjusting to the diagnosis. Support from a multidisciplinary team of allied health clinicians with experience in working with people with MS, such as physiotherapists, occupational therapists, continence specialists, exercise physiologists, speech pathologists, dietitians, psychologists and neuropsychologists, is important in managing specific symptoms in select individuals with MS (*R79*). To access allied health services in Australia, people with MS can be referred to their local rehabilitation or health services and use their Chronic Disease Management Plan through their general practitioner. People with MS younger than 65 years old may qualify for support services through the Australian National Disability Insurance Scheme (NDIS). Those older than 65 years who are not already under the NDIS are able to access My Aged Care Services. People with MS in New Zealand may be able to access funded allied health services via their local public hospital. A range of community allied health providers are available but these services are not fully funded.

Clinicians should exclude other causes of symptoms such as fatigue (eg, infection, depression, anaemia, iron deficiency, thyroid dysfunction) and consider non-pharmacological approaches (eg, exercise therapy for fatigue) before prescribing pharmacological therapy (*R80*). Medications commonly used for symptomatic treatment in MS are summarised in the Supporting Information (table 4). However, although widely recommended, evidence for these pharmacological treatments is lacking and most are not subsidised and, therefore, often expensive. For

example, a trial of methylphenidate, modafinil and amantadine for MS-related fatigue showed no benefit compared with placebo and the medications were associated with higher rates of adverse effects.[70]

Communication with general practitioners

Communication between neurologists and general practitioners is crucial in caring for people with MS. General practitioners can assist with risk mitigation on DMT, such as immunisations and routine cancer screening, as well as general health measures, such as assisting with smoking cessation, maintenance of a healthy diet and exercise, and monitoring cardiovascular health (see the sections "Risk mitigation strategies during treatment with disease-modifying therapy" and "General lifestyle measures").

Conclusion

These two-part guidelines provide a practical resource for clinicians on current best-practice recommendations for managing MS in the Australian and New Zealand health care settings. Future research is likely to influence these recommendations and, therefore, updated guidelines will be needed as additional research emerges and clinical practice changes. Application of these guidelines should be individualised to the unique needs, values, preferences and circumstances of the people with MS (Box).

Patient testament

"I've lived with MS for 20-plus years now and these guidelines bring me great relief … Life with MS is unreliable and inconsistent. Having confidence that your treating clinician understands your condition makes such a difference — whether that's your GP [general practitioner], the doctor you meet in emergency or a neurologist working outside the MS field."

Competing interests: Darshini Ayton is funded by a National Health and Medical Research Council (NHMRC) Emerging Leader Investigator Grant (APP1195357). She is living with MS and receives care and treatment from the Royal Melbourne Hospital. Heidi Beadnall has received honoraria for attendance at advisory boards and travel sponsorship from Biogen, Merck, Novartis, Roche and Sanofi–Genzyme, and speaking honoraria from Biogen, Merck, Novartis, Roche and Sanofi–Genzyme. She has been an investigator for clinical trials sponsored by Alexion, Biogen, Bristol Myers Squibb, Clene Nanomedicine, Merck, Novartis, Roche and Sanofi–Genzyme. Stefan Blum is and has been involved in clinical trials sponsored by Roche, Novartis, Sanofi–Genzyme, CSL, Clene Nanomedicine, Biogen and Merck. His institutions have received honoraria for advisory boards and speaking honoraria from Biogen, Merck, Roche and Novartis. Francesca Bridge has received travel compensation from Biogen and Novartis. 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 (GNT 1197339). 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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Jeannette Lechner-Scott received travel compensation from Biogen, Merck and Novartis and has been involved in clinical trials with Biogen, Merck, Novartis and Roche. Her institution has received honoraria for talks and advisory board service from Biogen, Merck, Novartis and Roche. Richard Macdonell or his institution has received remuneration for his speaking engagements, advisory board memberships, research and travel from Biogen, Merck, Sanofi–Genzyme, Bayer, Roche, Teva, Novartis, CSL, BMS, MedDay and NHMRC. Mark Marriott has received travel grants, speaking honoraria and unconditional research funding from Bayer, Biogen and Merck. Deborah Mason has received honoraria for advisory meetings with Roche and Biogen. Fiona McKay has received research funding from MS Research Australia, Trish MS Research Foundation, MND Research Institute of Australia, The Rebecca L Cooper Medical Research Foundation, the Australian Research Council, and NHMRC. Mastura Monif has served on the advisory board for Merck and Novartis, and has received speaker honoraria from Merck, Biogen and Novartis. Her institution receives funding from NHMRC (GNT2011590, MRF2030667, MRF1201062). Cassie Nesbitt has received speaker honoraria and or educational travel support from Merck, Biogen and Roche. Ai-Lan Nguyen has received speaker honoraria from Roche, Biogen, Teva, Merck Serono and Novartis. She has served on advisory boards for Merck Serono and Novartis. Sudarshini Ramanathan has received research funding from NHMRC, the Petre Foundation, the Brain Foundation, the Royal Australasian College of Physicians, and the University of Sydney. She is supported by an NHMRC Investigator Grant (GNT2008339). She serves as a consultant on an advisory board for UCB and Limbic Neurology, and has been an invited speaker for educational/research sessions coordinated by Biogen, Alexion, Novartis, Excemed and Limbic Neurology. She is on the medical advisory board (non-remunerated positions) of The MOG Project and the Sumaira Foundation. Louise Rath has received travel compensation and speaking honoraria from Novartis and Biogen. Stephen Reddel has received funds over the past five years, including, but not limited to, travel support, honoraria, trial payments, research and clinical support from bodies and charities: NHMRC, MRFF, NBA, Myasthenia Alliance Australia, Beeren foundation; and from pharmaceutical/biological companies: Alexion, Biogen, CSL, Genzyme, Grifols, Merck, Novartis, Roche, Sandoz, Sanofi, UCB. Additional interests and potential conflicts of interest include: co-founder/shareholder of RxPx health, National IVIG Governance Advisory Council and Specialist Working Group Australia (Neurology) (paid), Australian Medical Services Advisory Committee ad hoc subcommittee on IVIG (paid), Australian Technical Advisory Group on Immunisation Varicella Zoster working party (unpaid), public salary as a staff specialist neurologist from Concord Hospital Sydney Local Health District (paid), private billings from patients, and Medicare Australia reimbursement as a private practice neurologist (paid), medical advisor (unpaid) to various patient and advocacy groups. Izanne Roos served on scientific advisory boards, received conference travel support and/or speaker honoraria from Roche, Novartis, Merck and Biogen. She is supported by MS Australia and the Trish Multiple Sclerosis Research Foundation. Nabil Seery has received conference fee sponsorship from Roche. Marion Simpson has received support to attend educational meetings and speaker/board honoraria from the following companies: Biogen, Novartis, Merck, BioCSL, Bayer. Pakeeran Siriratnam has received travel support from Novartis and Biogen. has received speaker honoraria from Eisai and travel support from Biogen. Bruce Taylor served on scientific advisory boards, received conference travel support and/or speaker honoraria from Roche, Novartis, Merck and Biogen. He is supported by an NHMRC Leadership Fellowship (GNT2009389). Jennifer Taylor has received honoraria for attendance at advisory boards and travel sponsorship from Biogen, Novartis and Roche. Has been an investigator for clinical trials sponsored by Roche. Lisa Taylor has received conference travel support from Biogen, Merck, Novartis and Roche and nurse advisory consultant support from Novartis and Merck. Anneke van der Walt has received travel support and served on advisory boards for Novartis, Biogen, Merck and Roche, and she receives grant support from MS Australia and the NHMRC (GNT1196380). Wei Yeh has received speaker honoraria from Merck and Novartis. Michael Zhong has received conference travel support from Novartis and Roche, research support from the Australian Government Research Training Program and MS Research Australia, and speaking honoraria from Eisai.

Provenance: Not commissioned; externally peer reviewed. ■

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Supporting Information

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