

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

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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

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.

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 thrombocytopenia, 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.”

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Tomas Kalincik served on scientific advisory boards for MS International Federation and World Health Organization, BMS, Roche, Janssen, Sanofi–Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Roche, Sanofi–Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck. 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. 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1 Shipley J, Beharry J, Yeh W, et al. Consensus recommendations on multiple sclerosis management in Australia and New Zealand: part 1. *Med J Aust* 2024; <https://doi.org/10.5694/mja2.52578>.

2 US Food and Drug Administration. FDA drug safety communication: FDA warns about cases of rare brain infection with MS drug Gilenya (fingolimod) in two patients with no prior

exposure to immunosuppressant drugs. Silver Spring (MD): FDA, 2015. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-cases>

- rare-brain-infection-ms-drug-gilenya-fingo limod (viewed Aug 2023).
- 3 US Food and Drug Administration. FDA drug safety communication: FDA warns about case of rare brain infection PML with MS drug Tecfidera (dimethyl fumarate). Silver Spring (MD): FDA, 2014. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-case-rare-brain-infection-pml-ms-drug-tecfidera> (viewed Aug 2023).
- 4 Sriwastava S, Chaudhary D, Srivastava S, et al. Progressive multifocal leukoencephalopathy an sphingosine 1-phosphate receptor modulators used in multiple sclerosis: an updated review of literature. *J Neurol* 2022; 269: 1678-1687.
- 5 US Food and Drug Administration. Alemtuzumab: highlights of prescribing information. Silver Spring (MD): FDA, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103948s5172lbl.pdf (viewed Dec 2023).
- 6 Patel A, Sul J, Gordon ML, et al. Progressive multifocal leukoencephalopathy in a patient with progressive multiple sclerosis treated with ocrelizumab monotherapy. *JAMA Neurol* 2021; 78: 736.
- 7 Cortese I, Reich DS, Nath A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. *Nat Rev Neurol* 2021; 17: 37-51.
- 8 Hodel J, Darchis C, Outteryck O, et al. Punctate pattern: a promising imaging marker for the diagnosis of natalizumab-associated PML. *Neurology* 2016; 86: 1516-1523.
- 9 Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Eng J Med* 2012; 366: 1870-1880.
- 10 Major EO, Yousry TA, Clifford DB. Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. *Lancet Neurol* 2018; 17: 467-480.
- 11 Ho PR, Koendgen H, Campbell N, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. *Lancet Neurol* 2017; 16: 925-933.
- 12 Dunham SR, Schmidt R, Clifford DB. Treatment of progressive multifocal leukoencephalopathy using immune restoration. *Neurotherapeutics* 2020; 17: 955-965.
- 13 Landi D, De Rossi N, Zagaglia S, et al. No evidence of beneficial effects of plasmapheresis in natalizumab-associated PML. *Neurology* 2017; 88: 1144-1152.
- 14 Clifford DB, De Luca A, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol* 2010; 9: 438-446.
- 15 Mowry EM, Waubant E, McCulloch CE, et al. Vitamin D status predicts new brain magnetic resonance imaging activity in multiple sclerosis. *Ann Neurol* 2012; 72: 234-240.
- 16 Stamatellos VP, Rigas A, Stamoula E, et al. S1P receptor modulators in multiple sclerosis: detecting a potential skin cancer safety signal. *Mult Scler Relat Disord* 2022; 59: 103681.
- 17 Cancer Council Australia. Clinical guidelines: 16. Screening in immune-deficient women. Sydney: Cancer Council Australia, 2022. <https://www.cancer.org.au/clinical-guidelines/cervical-cancer/cervical-cancer-screening/screening-in-immun>
- e-deficient-women#:~:text=Screening%20interval%20recommendations&text=Immune%20deficient%20women%20who%20have,years%20with%20a%20HPV%20test (viewed Dec 2023).
- 18 Bridge F, Brotherton J, Stankovich J, et al. Risk of cervical abnormalities for women with multiple sclerosis treated with moderate-efficacy and high-efficacy disease-modifying therapies. *Neurology* 2024; 102: e208059.
- 19 Yeh WZ, Widyastuti PA, van der Walt A, et al. Natalizumab, fingolimod and dimethyl fumarate use and pregnancy-related relapse and disability in women with multiple sclerosis. *Neurology* 2021; 96: e2989-e3002.
- 20 Vukusic S, Hutchinson M, Hours M, et al. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. *Brain* 2004; 127: 1353-1360.
- 21 Krysko KM, Dobson R, Alroughani R, et al. Family planning considerations in people with multiple sclerosis. *Lancet Neurol* 2023; 22: 350-366.
- 22 Portaccio E, Moiola L, Martinelli V, et al. Pregnancy decision-making in women with multiple sclerosis treated with natalizumab: II: maternal risks. *Neurology* 2018; 90: e832-e839.
- 23 Hellwig K, Tokic M, Thiel S, et al. Multiple sclerosis disease activity and disability following cessation of fingolimod for pregnancy. *Neurol Neuroimmunol Neuroinflamm* 2023; 10: e200110.
- 24 Hughes SE, Spelman T, Gray OM, et al. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. *Mult Scler* 2014; 20: 739-746.
- 25 Landi D, Bovis F, Grimaldi A, et al. Exposure to natalizumab throughout pregnancy: effectiveness and safety in an Italian cohort of women with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2022; 93: 1306-1316.
- 26 Ebrahimi N, Herbristrit S, Gold R, et al. Pregnancy and fetal outcomes following natalizumab exposure in pregnancy. A prospective, controlled observational study. *Mult Scler* 2015; 21: 198-205.
- 27 Haghikia A, Langer-Gould A, Rellensmann G, et al. Natalizumab use during the third trimester of pregnancy. *JAMA Neurol* 2014; 71: 891.
- 28 Kämpfel T, Thiel S, Mehl I, et al. Anti-CD20 therapies and pregnancy in neuroimmunologic disorders: a cohort study from Germany. *Neurol Neuroimmunol Neuroinflamm* 2021; 8: e913.
- 29 Dobson R, Bove R, Borriello F, et al. Pregnancy and infant outcomes in women receiving ocrelizumab for the treatment of multiple sclerosis. 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; 13-15 Oct 2021 [virtual congress].
- 30 Hellwig K, Yamout B, Bove R, et al. Pregnancy outcomes in patients with multiple sclerosis following exposure to ofatumumab. American Academy of Neurology (AAN) 2022; Washington, DC (USA), 2-7 Apr 2022.
- 31 Dobson R, Rog D, Ovadia C, et al. Anti-CD20 therapies in pregnancy and breast feeding: a review and ABN guidelines. *Pract Neurol* 2023; 23: 6-14.
- 32 Giannini M, Portaccio E, Ghezzi A, et al. Pregnancy and fetal outcomes after glatiramer acetate exposure in patients with multiple sclerosis: a prospective observational multicentric study. *BMC Neurol* 2012; 12: 124.
- 33 Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000; 62: 385-392.
- 34 Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. *Rheum Dis Clin North Am* 2017; 43: 489-502.
- 35 Eastwood K, Mohan AR. Imaging in pregnancy. *Obstet Gynecol* 2019; 21: 255-262.
- 36 Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. *N Eng J Med* 1998; 339: 285-291.
- 37 Krysko KM, Rutatangwa A, Graves J, et al. Association between breastfeeding and postpartum multiple sclerosis relapses: a systematic review and meta-analysis. *JAMA Neurol* 2020; 77: 327-328.
- 38 Ciplea AI, Langer-Gould A, Stahl A, et al. Safety of potential breast milk exposure to IFN- β or glatiramer acetate: one-year infant outcomes. *Neurol Neuroimmunol Neuroinflamm* 2020; 7: e757.
- 39 Ciplea AI, Langer-Gould A, de Vries A, et al. Monoclonal antibody treatment during pregnancy and/or lactation in women with MS or neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm* 2020; 7: e723.
- 40 Gklinos P, Dobson R. Monoclonal antibodies in pregnancy and breastfeeding in patients with multiple sclerosis: a review and an updated clinical guide. *Pharmaceuticals (Basel)* 2023; 16: 770.
- 41 Langer-Gould AM. Pregnancy and family planning in multiple sclerosis. *Continuum (Minneapolis)* 2019; 25: 773-792.
- 42 Simpson-Yap S, De Brouwer E, Kalinick T, et al. Associations of disease-modifying therapies with COVID-19 severity in multiple sclerosis. *Neurology* 2021; 97: e1870-e1885.
- 43 Melamed E, Lee MW. Multiple sclerosis and cancer: the ying-yang effect of disease modifying therapies. *Front Immunol* 2020; 10: 2954.
- 44 Fitzgerald KC, Munger KL, Köchert K, et al. Association of vitamin D levels with multiple sclerosis activity and progression in patients receiving interferon beta-1b. *JAMA Neurol* 2015; 72: 1458-1465.
- 45 Halabchi F, Alizadeh Z, Sahraian MA, Abolhasani M. Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. *BMC Neurol* 2017; 17: 185.
- 46 Albergoni M, Storelli L, Preziosa P, et al. The insula modulates the effects of aerobic training on cardiovascular function and ambulation in multiple sclerosis. *J Neurol* 2023; 270: 1672-1681.
- 47 Kalb R, Brown TR, Coote S, et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. *Mult Scler* 2020; 26: 1459-1469.
- 48 Dalgas U, Stenager E, Ingemann-Hansen T. Review: multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. *Mult Scler* 2008; 14: 35-53.
- 49 Katz Sand I, Benn EKT, Fabian M, et al. Randomized-controlled trial of a modified Mediterranean dietary program for multiple sclerosis: a pilot study. *Mult Scler Relat Disord* 2019; 36: 101403.

- 50 Irish A, Erickson C, Wahls T, et al. Randomized control trial evaluation of a modified Paleolithic dietary intervention in the treatment of relapsing-remitting multiple sclerosis: a pilot study. *Degener Neurol Neuromuscul Dis* 2017; 7: 1-18.
- 51 Choi IY, Piccio L, Childress P, et al. A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. *Cell Rep* 2016; 15: 2136-2146.
- 52 Brenton JN, Banwell B, Bergqvist AGC, et al. Pilot study of a ketogenic diet in relapsing-remitting MS. *Neurol Neuroimmunol Neuroinflamm* 2019; 6: e565.
- 53 Brenton JN, Lehner-Gulotta D, Woolbright E, et al. Phase II study of ketogenic diets in relapsing multiple sclerosis: safety, tolerability and potential clinical benefits. *J Neurol Neurosurg Psychiatry* 2022; 93: 637-644.
- 54 Parks NE, Jackson-Tarlton CS, Vacchi L, et al. Dietary interventions for multiple sclerosis-related outcomes. *Cochrane Database Syst Rev* 2020; (5): CD004192.
- 55 Spain R, Powers K, Murchison C, et al. Lipoic acid in secondary progressive MS: a randomized controlled pilot study. *Neurol Neuroimmunol Neuroinflamm* 2017; 4: e374.
- 56 Tourbah A, Lebrun-Frenay C, Edan G, et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study. *Mult Scler* 2016; 22: 1719-1731.
- 57 MedDay Pharmaceuticals. MedDay reports top-line data from phase III trial "SPI2" for treatment of progressive forms of multiple sclerosis. Paris: MedDay, 2023. <http://www.medday-pharma.com/2020/03/10/medday-reports-top-line-data-from-phase-iii-trial-spi2-for-treatment-of-progressive-forms-of-multiple-sclerosis/> (viewed Aug 2023).
- 58 Hernán MA, Jick SS, Logroschino G, et al. Cigarette smoking and the progression of multiple sclerosis. *Brain* 2005; 128: 1461-1465.
- 59 Di Pauli F, Reindl M, Ehling R, et al. Smoking is a risk factor for early conversion to clinically definite multiple sclerosis. *Mult Scler* 2008; 14: 1026-1030.
- 60 O'Gorman CM, Broadley SA. Smoking increases the risk of progression in multiple sclerosis: a cohort study in Queensland, Australia. *J Neurol Sci* 2016; 370: 219-223.
- 61 Butzkueven H, Ponsonby AL, Stein M, et al. Vitamin D did not reduce multiple sclerosis disease activity after a clinically isolated syndrome. *Brain* 2024; 147: 1206-1215.
- 62 McLaughlin L, Clarke L, Khalilidehkordi E, et al. Vitamin D for the treatment of multiple sclerosis: a meta-analysis. *J Neurol* 2018; 265: 2893-2905.
- 63 Dörr J, Bäcker-Koduah P, Wernecke KD, et al. High-dose vitamin D supplementation in multiple sclerosis — results from the randomized EVIDIMS (efficacy of vitamin D supplementation in multiple sclerosis) trial. *Mult Scler J Exp Transl Clin* 2020; 6: 2055217320903474.
- 64 Hearn AP, Silber E. Osteoporosis in multiple sclerosis. *Mult Scler* 2010; 16: 1031-1043.
- 65 Opara JA, Brola W, Wylegala AA, Wylegala E. Uhthoff's phenomenon 125 years later — what do we know today? *J Med Life* 2016; 9: 101-105.
- 66 Filippini G, Brusafferri F, Sibley WA, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. *Cochrane Database Syst Rev* 2000; (4): CD001331.
- 67 Burton JM, O'Connor PW, Hohol M, Beyene J. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. *Cochrane Database Syst Rev* 2012; (12): CD006921.
- 68 Liu S, Liu X, Chen S, et al. Oral versus intravenous methylprednisolone for the treatment of multiple sclerosis relapses: a meta-analysis of randomized controlled trials. *PLoS One* 2017; 12: e0188644.
- 69 Berkovich R. Treatment of acute relapses in multiple sclerosis. *Neurotherapeutics* 2013; 10: 97-105.
- 70 Nourbakhsh B, Revirajan N, Morris B, et al. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. *Lancet Neurol* 2021; 20: 38-48. ■

Supporting Information

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