# Twenty years of natalizumab in multiple sclerosis: lessons learned and future outlook

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Abstract: Twenty years on from its initial approval as the first monoclonal antibody for the treatment of multiple sclerosis (MS), natalizumab remains a valuable high-efficacy treatment option for people with relapsing-remitting MS, with robust real-world evidence supporting its long-term efficacy and well-characterized safety profile, provided that the risk of progressive multifocal leukoencephalopathy (PML) is monitored and mitigated. This review explores the long-term clinical impact of natalizumab. It draws on two decades of experience to guide treatment strategies with natalizumab, including its use early in the disease course, switching to natalizumab, its use during vaccination, and PML risk management and exit strategies. Guidance on the use of natalizumab in pregnant and breastfeeding women with MS, children with MS, and people with comorbidities is discussed, along with reflections on what has been learned from 20 years with natalizumab, and what the future holds for this impactful treatment in MS and beyond.

Graphical abstract

20 years of natalizumab: writing the next chapter

As the first monoclonal antibody approved for MS, natalizumab has **two decades of long-term evidence** supporting its real-world efficacy and safety. It remains a valuable HET option for people with RRMS

Natalizumab has a **unique mode of action**, selectively compromising the immune response in the CNS by inhibiting leukocyte migration into the CNS

This distinct mode of action provides the unique benefits of **rapid onset of action and reversibility**

These attributes of **natalizumab** may be particularly useful in specific populations, such as...
- Those pregnant and breastfeeding
- People with comorbidities
- People receiving vaccinations

What have we learned from natalizumab?

Early use of HET, including natalizumab, has improved patient outcomes, shifting the treatment paradigm away from the traditional escalation treatment strategy

Management of the two biggest risks with natalizumab: PML and disease activity rebound
- Development of the first structured risk management plan in MS has led to reduced PML incidence over time
- Risk of rebound can be mitigated by timely initiation of another HET

What does the future hold for natalizumab?
- Potential for genetic testing to better understand PML risk
- Potential for use in new indications

Abbreviations: **CNS**, central nervous system; **HET**, high-efficacy treatment; **MS**, multiple sclerosis; **PML**, progressive multifocal leukoencephalopathy; **RRMS**, relapsing-remitting multiple sclerosis

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Introduction

In 2004, natalizumab became the first monoclonal antibody approved to treat multiple sclerosis (MS),[1,2] marking the second major milestone in the MS treatment landscape following the introduction of the first interferon (IFN) treatment in 1993.[1,3] Twenty years on, the long-term efficacy and well-characterized safety profile of natalizumab is supported by robust real-world evidence (RWE).[4,5] Natalizumab has a unique mode of action,[6] selectively compromising the immune response in the central nervous system (CNS) and gut.[7] This results in low rates of opportunistic infections,[4] provided that the risk of progressive multifocal leukoencephalopathy (PML) is monitored and mitigated.[8] This, combined with the recent approval of biosimilar natalizumab by the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA),[9–11] which could see natalizumab become more accessible at a lower cost to healthcare systems,[12] means that it remains a valuable treatment option for MS and may hold promise for people with unmet medical need.[13]

MS is a chronic, progressive, autoimmune disease affecting the brain and spinal cord and is characterized by inflammatory and neurodegenerative processes.[14,15] Symptoms include those affecting motor and sensory function (e.g., weakness, spasticity, ataxia, and altered sensation),[16,17] vision,[18] speech/swallowing,[19] bladder, and bowel.[20,21] MS can also cause fatigue, cognitive, and mood symptoms.[14] MS affects around 2.3 million people worldwide and is usually diagnosed between the ages of 20 and 50[22]; however, between 3% and 10% of cases are diagnosed in children under the age of 16.[23] The 2024 updates to the McDonald criteria for diagnosis of MS are expected to help clinicians make accurate diagnosis at an earlier stage of the disease.[24]
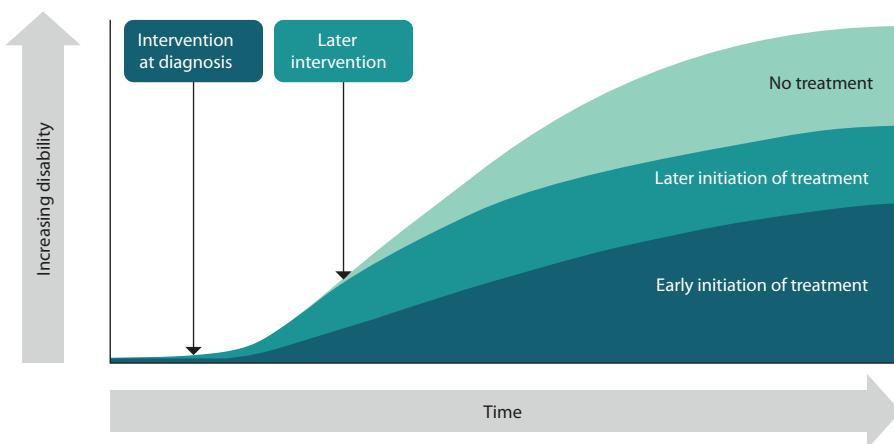
Relapsing-remitting MS (RRMS) is the most common clinical phenotype, occurring in approximately 85% of people with MS, and it is characterized by alternating periods of distinct relapse and full or partial recovery of neurological function, with relapse-associated worsening of disability.[25] However, even from the early phases of RRMS, the majority of disability progression is progression independent of relapse activity (PIRA), which is the predominant driver of disability accumulation.[26,27]

Current treatment strategies aim to reduce the risk of relapses, and potentially, disability progression, with treatment response assessed via clinical measures and magnetic resonance imaging (MRI) activity.[3] Treatment objectives for people with MS include the prevention of novel disease activity based on clinical and imaging features, which is termed "no evidence of disease activity (NEDA)" as well as "minimal evidence of disease activity."[28] In this line, a retrospective analysis from the natalizumab AFFIRM clinical trial was the first to use freedom from disease activity as a measure of treatment efficacy and showed that disease remission could be an attainable treatment goal in MS.[29,30]

Over the past three decades, there has been a large increase in the number of therapeutic options available for MS,[3] with around 20 disease-modifying therapies (DMTs) currently approved by the FDA and/or the EMA.[31–33] The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and European Academy of Neurology (EAN) guidelines recommend early treatment with DMTs for people with active RRMS, choosing between the wide range of available drugs from those that are "moderately effective" to "highly effective."[3]

Two distinct treatment strategies are often used in MS: (1) escalation, which involves starting treatment with limited efficacy, low side effect treatment options, and then switching to a high-efficacy treatment (HET), with potentially more side effects, if necessary, and (2) the early initiation of HET.[34,35] Early use of DMTs is associated with better long-term treatment outcomes (Figure 1(a)); however, early use of HET, including alemtuzumab, natalizumab, ocrelizumab, ofatumumab, and off-label rituximab, has not only been demonstrated to provide a greater reduction in relapse rates than lower-efficacy DMTs, such as IFN beta and glatiramer acetate, but more recent evidence shows that treating early with an HET also results in better long-term outcomes in terms of disability accumulation.[34,36–39] Additionally, RWE supports the use of natalizumab early in the disease course (Figure 1(b)), as a study of people who initiated treatment with either natalizumab or a lower-efficacy DMT after their MS diagnosis found that those initiating natalizumab were less likely to experience a relapse during the follow-up period.[40] Early use of natalizumab is discussed further in

(a)

(b)
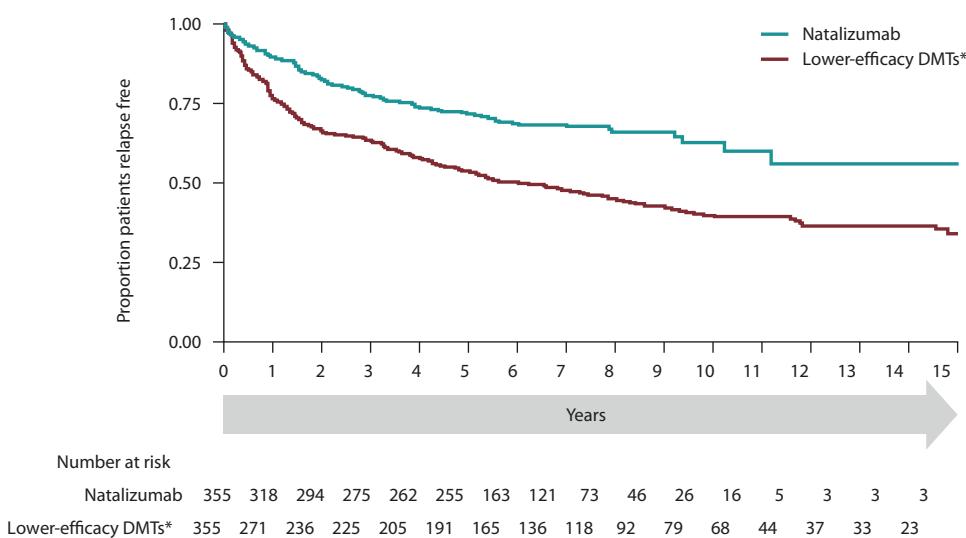
Figure 1. Long-term prognosis with (a) earlier versus later initiation of treatment and (b) early initiation of natalizumab versus lower-efficacy DMTs.
Source: Part (a) adapted with permission from Giovannoni et al.[41] (p. 19, Figure 10). Part (b) is reproduced with permission from Butzkueven et al.[40] (p. 6, Figure 1).
*Lower-efficacy DMT refers to treatment with IFN beta, glatiramer acetate, teriflunomide, or dimethyl fumarate.
DMT, disease-modifying therapy; HET, high-efficacy treatment; IFN, interferon.

the section of this article, "Practical guidance on the clinical use of natalizumab."

Natalizumab: Mode of action

Natalizumab is a humanized anti-$\alpha 4\beta 1$ integrin monoclonal antibody[42] that was approved by the FDA in 2004[2] for the treatment of adults with relapsing forms of MS,[43] and by the EMA in 2006 for the treatment of adults with highly active RRMS.[44] A biosimilar, a biological medicine that has no clinically meaningful differences in quality, safety, and efficacy versus an already licensed reference biological medicine, has been developed for natalizumab and was approved for these same indications by the FDA and EMA in 2023.[9–11,45]
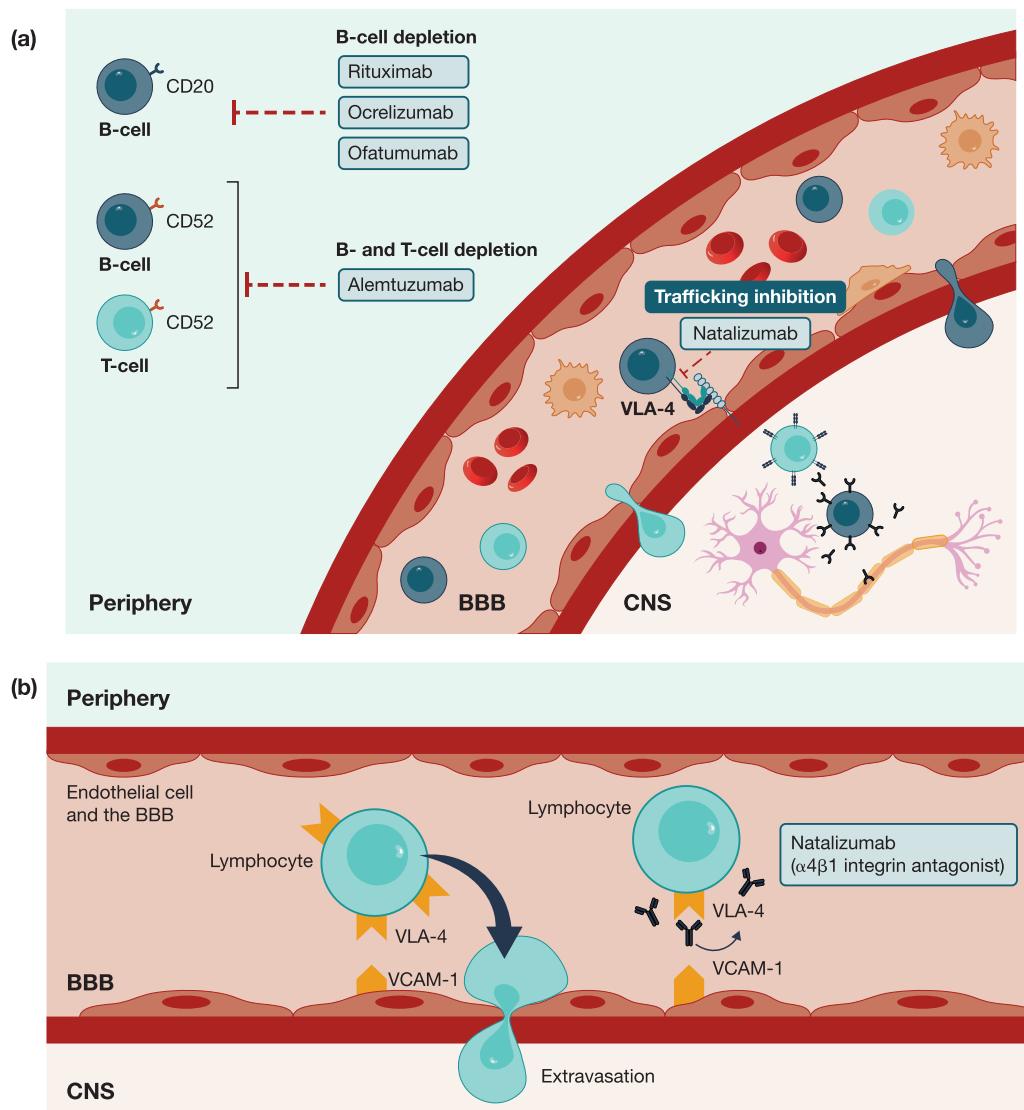
Figure 2. Mode of action for (a) high-efficacy DMTs for MS and (b) natalizumab specifically.
Source: Part (a) is adapted from Yang et al.[6] (p. 9; Figure 1). Part (b) is adapted from Sheremata et al.[42] (p. 6; Figure 1).
BBB, blood–brain barrier; CD, cluster of differentiation; CNS, central nervous system; DMT, disease-modifying therapy; MS, multiple sclerosis; VCAM-1, vascular cellular adhesion molecule 1; VLA-4, very late antigen-4.

Natalizumab and its biosimilar are also approved by the FDA to treat Crohn's disease.[10,11,43]

Figure 2 shows the mode of action of a range of high-efficacy DMTs used to treat MS. Natalizumab has a distinct and unique mode of action from other HET used in MS[6] (Figure 2(a) and (b)).

Unlike treatments that cause long-term B-cell depletion, natalizumab prevents leukocytes from entering the brain and spinal cord by blocking the interaction between $\alpha4\beta1$ integrin and VCAM-1, preventing leukocytes from crossing the blood-brain barrier (BBB).[42] This inhibition of leukocyte migration into the CNS reduces new MS lesion formation.[42,46,47] Natalizumab may also inhibit ongoing inflammation by disrupting the interactions between inflammatory leukocytes and extracellular matrix proteins,[48] or by inducing apoptosis of activated T cells.[49] Additionally, natalizumab treatment has been shown to indirectly impact microglial activation in the brain, a process considered to be associated with MS

disease progression; a recent study of 21 people with MS found that microglial activation was reduced following 1 year of treatment with natalizumab.[50]

Furthermore, natalizumab may have other immunological effects beyond VLA-4 interaction: an observational longitudinal cohort study of 22 people with RRMS found an increase in anti-inflammatory cytokines just a few hours to days after the first intravenous (IV) infusion of natalizumab,[51] and a recent meta-anlaysis has shown that natalizumab can lead to a reduction in intrathecal oligoclonal bands in cerebrospinal fluid, suggesting a possible effect on memory plasma cells.[52]

Unique properties and clinical impact of natalizumab

The efficacy of natalizumab in people with RRMS was demonstrated in the phase III AFFIRM trial, with a significant reduction in relapse rate, disease activity, and disability progression versus placebo.[53] The phase III SENTINEL trial also confirmed that natalizumab in combination with IFN beta-1a was significantly more effective than IFN beta-1a alone; however, natalizumab was only approved as a monotherapy.[43,54] With almost two decades of experience, natalizumab is now a well-established and well-characterized treatment,[55] which offers a range of benefits to people with RRMS. Not only does natalizumab provide long-term clinical effectiveness, but also, because of its distinct mode of action, natalizumab exhibits unique properties compared with other MS treatments, in particular, rapid onset of action and reversibility.

Rapid onset of action

Natalizumab treatment has a rapid onset of action. In a study of the effect of a single dose of natalizumab administered soon after the onset of an MS relapse, changes in MRI activity were noted as early as 1 week after dosing.[56] In AFFIRM, a significant reduction in the cumulative risk of relapse was observed early, within 8 weeks, and a significant reduction in the annualized relapse rate (ARR) was observed within 3 months.[57] The rapid action of natalizumab may be explained by its unique mode of action, with the inhibition of leukocyte migration into the CNS preventing lesion formation.[57]

Comparing HET options, the phase IV REVEAL study, which investigated natalizumab versus fingolimod in people with RRMS, found that the effect on disease activity was more rapid with natalizumab than with fingolimod and that T1 gadolinium-enhancing lesion accumulation was lower with natalizumab than with fingolimod at 4 weeks (63% lower at 4 weeks ($p = 0.353$), $\geqslant 70\%$ lower at 12 weeks ($p = 0.030$), which was maintained at 24 weeks ($p = 0.008$)).[58] Additionally, a study assessing the effect of natalizumab versus ocrelizumab on quality-of-life (QoL) outcomes in people with MS found that those treated with natalizumab experienced a shorter time to clinically meaningful improvement in several QoL domains, including cognitive function, compared with ocrelizumab (event time ratio (95% confidence interval (CI)): 0.37 (0.24–0.57); $p < 0.001$).[59] In two other studies, the effect of ocrelizumab on disability progression[60] and ofatumumab on disability progression and ARR[61] were not measured until 12 weeks after the first dose,[60,61] although a phase II study of ofatumumab showed rapid B-cell depletion within 14 days.[62] Rituximab was found to reduce the number of gadolinium-enhancing lesions from 12 weeks after the first dose, compared with placebo.[63]

Reversibility. Given the wide range of therapies available to people with RRMS, clinicians should consider the temporal nature and reversibility of a treatment's biological effects, as this could impact treatment sequencing should someone need to switch to a new treatment.[64]

The effects of natalizumab on peripheral immune cells and pharmacodynamic markers are reversible, with both peripheral immune cell count and pharmacodynamic marker levels starting to decline 8–12 weeks after the final natalizumab dose, returning to pre-treatment levels by 16 weeks.[64] The risk of rebound MS disease upon cessation of natalizumab and guidance on exit strategies is discussed in the section on "Exit strategies in people with high PML risk."

The reversibility of natalizumab treatment is in contrast to other HET immunotherapies available for RRMS that act to deplete specific cell populations, such as alemtuzumab and ocrelizumab, where reconstitution of depleted B- or T-cell populations can take 9 months or longer.[64] This

can present an issue for treatment sequencing, as long-lasting effects on the immune system could present safety concerns when using sequential treatments.[65] However, after discontinuation of natalizumab, the rapid reconstitution of the peripheral immune system may allow increased flexibility in treatment sequencing.[64]

Long-term clinical effectiveness. As the first monoclonal antibody to be approved for MS,[1] natalizumab benefits from the longest period of RWE of any HET for MS, with several studies demonstrating the long-term clinical effectiveness of natalizumab. The Tysabri Observational Program (TOP) 10-year interim analysis included 6148 people with RRMS and found that the reduction in ARR seen after 1 year was sustained over 10 years of natalizumab treatment.[4] Additionally, an Austrian study of 1596 people found that ARR reduction on natalizumab was sustained over a follow-up time of up to 14 years.[66]

Confirmed disability improvement (CDI) was first described in a post hoc analysis of the AFFIRM trial where natalizumab increased the probability of 3-month CDI over 2 years compared with placebo.[67,68] A separate TOP analysis including 5384 people with RRMS found that disability improvement on natalizumab could be sustained over 8 years.[69] Furthermore, the TOP 10-year interim analysis found that at 10 years, the cumulative probability of 24-week CDI was 33.1%, and Expanded Disability Status Scale (EDSS) scores remained stable over 10 years of treatment with natalizumab.[4]

A study from Denmark, which followed 2424 people treated with natalizumab across a 13-year time period, found strong RWE for efficient suppression of clinical relapses, EDSS worsening, and radiological activity.[70] Notably in this study, MRI disease activity (defined as any new/enlarging T2 lesions or any gadolinium-enhancing lesions) was rare in people treated with natalizumab, with just 2.7% of people showing signs of MRI activity between 26 and 38 months after treatment initiation.[70] An extensive observational study of people with MS treated with natalizumab in Spain found that, among the 825 people treated with natalizumab for at least a year, there was a significant decrease in EDSS score, with the mean EDSS score decreasing from 3.71 (95% CI 3.60–3.82) at baseline to 3.37 (95% CI 3.25–3.49) after 12 months of treatment.[5] The effect of natalizumab

on disability improvement may be linked, according to the author's opinion, to its suppression of the evolution of new gadolinium-enhancing to T1-hypointense lesions and a reduction of axonal degeneration in relapsing forms of MS.[71,72]

Health-related QoL improvements. In addition to the long-term efficacy data on the prevention of relapse, disability accumulation, and disability improvement described above, natalizumab has been shown to improve health-related quality of life (HRQoL) significantly in both clinical trial[73,74] and real-world[75,76] settings. In particular, a study of 195 people who had been prescribed natalizumab highlighted the value of patient-reported outcomes in assessing the potential benefits of natalizumab and found that the majority of people (>92%) had stable or improved total, motor, and cognitive fatigue after 1 year of treatment.[77]

Comparisons with other HETs. The efficacy of natalizumab has been compared to other HET options in several studies. In the BEST-MS prospective study of 223 people with RRMS, significantly more people treated with natalizumab had NEDA after 1 year versus those treated with fingolimod.[78] Another real-world study of 174 people comparing natalizumab with fingolimod found that a significantly greater proportion of people treated with natalizumab had NEDA after 4 years compared to those treated with fingolimod.[79] In a retrospective observational cohort study, which included 740 people with RRMS, natalizumab had a similar effect to anti-CD20 therapy (rituximab or ocrelizumab) on relapse rate and disability progression in people switching from fingolimod.[80] Furthermore, a study of the MSBase cohort comparing cladribine to other immunotherapies for MS found that cladribine was associated with a higher ARR than natalizumab, and the risk of disability worsening was lower in people treated with natalizumab than in those treated with cladribine.[81] Taken together, these studies indicate that natalizumab has improved efficacy with respect to the outcomes studied versus fingolimod or cladribine and comparable efficacy versus anti-CD20 therapies.

Safety and tolerability of natalizumab

Long-term safety and tolerability

Natalizumab demonstrated a favorable safety and tolerability profile within the 2-year evaluation period of the phase III AFFIRM study, with

both serious adverse events (SAEs) and overall infection rates similar between people receiving natalizumab and those receiving placebo.[53] Real-world, long-term safety data are consistent with the results of the AFFIRM clinical trial: in the 10-year analysis of TOP, over 85% of people who received natalizumab did not experience any SAEs.[4] The most common SAEs were infections and infestations (4.1%); malignancy rates were 1.1%, and while breast cancer was the most frequent malignancy, it occurred at a rate of 86.7 per 100,000 patient-years, which is lower than the expected European age-standardized incidence rate of 94.2 per 100,000.[4] The incidence of PML in the TOP cohort was 0.9%, and the incidence of non-PML opportunistic infections was 0.2%,[4] which included herpes zoster, herpes meningitis, encephalitis, herpes simplex encephalitis, herpes zoster disseminated, listeria meningitis (sepsis), pneumonia, and pulmonary *Mycobacterium kansasii* infection.[4] In rare cases, natalizumab may increase the risk of herpes simplex virus reactivation in the CNS, leading to herpes encephalitis; however, these infections may present with atypical clinical features.[82–84]

Anti-natalizumab antibodies

Because natalizumab is a biologic treatment, some people develop anti-natalizumab antibodies, a fraction of which are persistent and have the potential to neutralize the drug's effect.[85] In the AFFIRM trial, 57 people receiving natalizumab (9%) had detectable anti-natalizumab binding antibodies at some time during the study.[53] Of these, persistent antibodies developed in 37 people (6%), and these people had an increase in infusion-related adverse events (AEs) and a loss of efficacy of natalizumab.[53] A retrospective observational study of 1251 people with MS who had experienced either an infusion-related event (IRE) or disease exacerbation while receiving natalizumab found that 12.3% of this cohort had detectable anti-natalizumab antibodies.[85] These antibodies were typically detected earlier in the treatment course, with anti-natalizumab antibodies more frequently detected during the first six infusions.[85] Anti-natalizumab antibodies were more frequently detected among people with IREs compared to those with disease exacerbation (21.6% vs 10.8%), suggesting that anti-natalizumab antibodies may have an impact on the development of IRE and, to a lesser extent, disease exacerbation.[85] When a drug is released

to the market, as in the case of natalizumab, anti-drug antibody testing may add to a risk-minimization plan (for IRE and anaphylactic reactions), shorten the time that people stay on treatment with a drug that is not effective for them, and consequently promote beneficial therapeutic switches.[86] However, persistent disease activity while taking natalizumab would result in a change of treatment strategy. This would make anti-natalizumab antibody testing unnecessary, although testing for anti-drug antibodies may indicate loss of treatment function in people with stable disease, thus enabling an early treatment change.

In the authors' experience, anti-drug antibody testing strategies in clinical practice vary significantly by geographic region and are not always available. For example, in Denmark anti-drug antibodies are routinely tested at 3, 6, and 12 months, and if possible, re-analyzed 1–3 months later, while authors from Austria, Germany, and the UK only routinely test at 12 and 24 months into treatment if the person with MS experiences infusion reactions, and if there is an early lack of efficacy. In Sweden, anti-drug antibodies are tested only in those with an infusion-related reaction and in cases of treatment failure. However, many health-care professionals (HCPs) are not regularly testing, as when adverse reactions or a lack of efficacy is experienced, a switch in treatment strategy would be considered regardless.

PML risk management

PML infection is an important safety concern related to natalizumab treatment.[87] It is an opportunistic CNS infection caused by the John Cunningham (JC) virus that can be fatal or result in severe disability.[9,44,88] PML most commonly occurs in people with HIV infection, lymphoproliferative disease, and in people who are receiving natalizumab, and can also occur in association with other drugs, such as those used for organ transplantation.[89] Other drugs have been associated with a risk of PML, including other HETs for MS[89]; however, the prevalence of PML in people with MS taking other DMTs is much lower than that associated with natalizumab.[88] Proposed mechanisms of action underlying the increased risk of PML in people taking natalizumab include reduction of JC virus-related CNS immunosurveillance by prevention of JC virus-specific cytotoxic T-cell entry into CNS tissue or

other sites where JC virus may be dormant and blocking of α4β1 integrin receptors, leading to the release of B cells from bone marrow and spleen, which is the common site of JC virus latency.[90] In either case, reactivation of latent JC virus by the action of natalizumab then triggers the development of PML.[90] For diagnosis of PML, an evaluation including a gadolinium-enhanced MRI scan of the brain and, for confirmation, cerebrospinal fluid analysis for JC virus DNA is required.[43,91,92]

Following the approval of natalizumab by the FDA in November 2004, two cases of PML in people who had received natalizumab in the SENTINEL trial (which evaluated the safety and efficacy of natalizumab in combination with IFN beta-1a) led to the withdrawal of natalizumab from the market in February 2005.[54,93] However, in June 2006, the FDA approved the reintroduction of natalizumab with revised labeling and improved safety warnings for PML risk management.[93,94] In the TOP cohort ($n = 6148$), only 53 (0.9%) people had developed confirmed PML over 10 years, which equates to an incidence rate of 2.034 per 1000 patient-years.[4]

The main risk factors for PML are JC virus antibody serum positivity, prior immunosuppressive treatment, and natalizumab treatment duration beyond 24 months.[95] PML risk stratification based on JC virus serologic test results, prior immunosuppressant use, and duration of natalizumab treatment, coupled with close monitoring and education, have reduced the incidence of natalizumab-associated PML in people with MS over recent years; for example, in Sweden, cumulative PML incidence fell from a high of 1.49 events per 1000 person years in 2012 to 0.72 in 2018.[8,95] Figure 3 shows a guide to mitigating PML risk.

Extended interval dosing, where natalizumab is given every 6 weeks (QW6) rather than every 4 weeks (QW4; standard interval dosing), is an emerging strategy in PML risk management, as the partial desaturation of α integrin receptors may enhance immune surveillance within the CNS and subsequently reduce the risk of PML.[99] A retrospective cohort study using a large dataset, the Tysabri Outreach: Unified Commitment to Health (TOUCH) program, has shown that extended interval dosing lowers PML risk compared with standard interval dosing.[100] When

moving to extended interval dosing, several studies have shown no reduction in the efficacy of natalizumab when moving to extended interval dosing in relation to MRI activity and relapses.[101,102] In particular, the phase III NOVA study comprising 499 people with RRMS who had been treated with natalizumab Q4W without relapse for 1 year or more and randomized to switch to natalizumab Q6W or remain on natalizumab Q4W concluded that the majority of people stable on natalizumab Q4W dosing can switch to Q6W without a clinically meaningful loss of efficacy.[103] Furthermore, another study of 73 people with RRMS demonstrated that extended interval dosing in people with RRMS did not increase axonal damage, as determined by serum neurofilament light chain concentrations.[104] However, the efficacy of natalizumab when administered by extended interval dosing still needs to be fully determined. Therefore, the benefit/risk balance of extended interval dosing is unknown.[44]

Exit strategies in people with high PML risk. A switch to an alternative treatment in people with MS who respond to natalizumab but are exposed to a higher PML risk based on the anti-JC virus index level represents an important therapeutic challenge in clinical practice.[41,105] In cases where natalizumab should be discontinued, it is important to have a clear exit strategy, as there is a risk of reactivation of MS disease activity in people who have stopped natalizumab treatment, particularly in those with a longer treatment gap after its withdrawal.[106] This risk of rebound can be mitigated by timely initiation of another HET after cessation of natalizumab.[106,107] In the experience of the authors, the washout period should be no greater than 8 weeks, and as early as 4–6 weeks, or even sooner as long as the person has immunocompetence. Furthermore, the risk of carryover PML (PML that develops a few months after stopping natalizumab treatment and starting an alternative DMT) should also be thought of.[41] To lower this risk, lower-efficacy oral maintenance therapies may occasionally be considered to bridge patients before switching to another treatment option.[41]

A systematic review indicated that anti-CD20 monoclonal antibody therapy is a suitable option after natalizumab treatment, with the demonstration of low rates of relapse and carryover PML.[108] The at-risk period for carryover PML is probably less than 12 months after switching
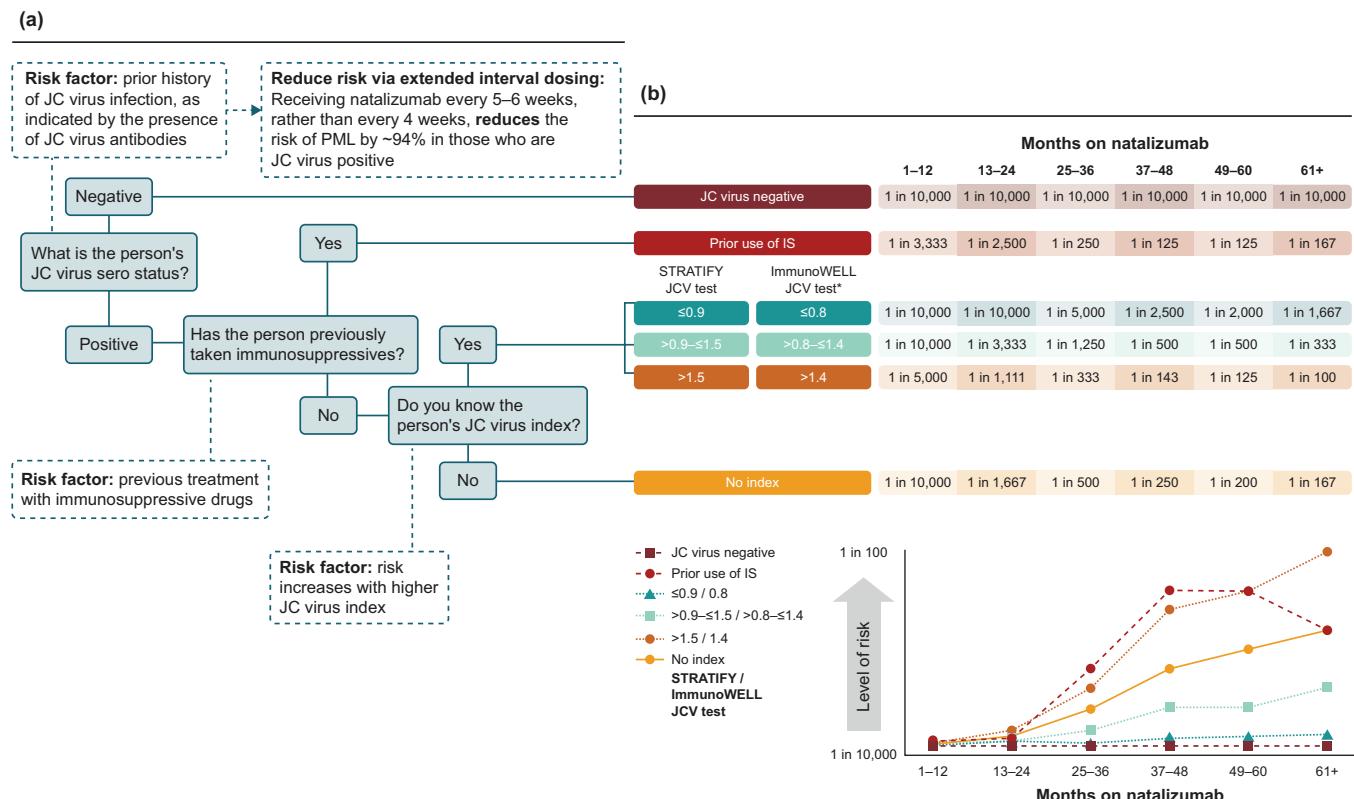
Figure 3. PML risk explained: (a) how to assess PML risk in people with MS and (b) PML risk over time.
Source: Figure is adapted from Biogen,[96] Ho et al.,[97] and Giovannoni.[98]
*An assay that uses a two-step ELISA process for qualitative detection of anti-JC virus antibodies in human serum.
ELISA, enzyme-linked immunosorbent assay; IS, immunosuppressant; JC, John Cunningham; JCV, John Cunningham virus; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

from natalizumab.[41] Furthermore, two observational, retrospective studies have shown ocrelizumab specifically to be an effective exit strategy after natalizumab discontinuation.[105,109] The first study demonstrated ocrelizumab to be superior to fingolimod, with a 70% lower relapse rate at 1 year[109]; the second study showed a lower risk of relapses and new MRI activity for people switching from natalizumab to ocrelizumab versus cladribine.[105] The reversibility of natalizumab allows for increased flexibility in treatment sequencing,[64] as discussed in the section on "Reversibility."

Practical guidance on the clinical use of natalizumab

Treatment strategies

IV and subcutaneous administrations. Natalizumab was first approved in 2004 as 300 mg IV infusion Q4W,[2] with subcutaneous (SC) administration approved by the EMA in 2021[44,110]

following the pivotal DELIVER and REFINE randomized controlled trials,[111,112] where the FDA has yet to approve.[43] Both DELIVER and REFINE demonstrated SC-natalizumab to be reasonably comparable to IV-natalizumab in regards to pharmacokinetics/dynamics, with REFINE also showing comparable safety and efficacy between the two formulations,[111,112] and a post hoc analysis of REFINE has further demonstrated comparable efficacy with IV-natalizumab by reporting non-inferiority of natalizumab SC on ARR.[113] However, there have been some concerns regarding low drug concentrations with SC administration, potentially affecting those on extended interval dosing or those with a higher body mass index (BMI),[114,115] suggesting that SC administration may not be the right application for these individuals. Regarding extended interval dosing, a retrospective study comparing the performance of extended interval dosing versus standard interval dosing found no difference in the primary analysis, though an exploratory BMI

analysis revealed a potential interaction between high BMI and disease activity in those treated with extended interval dosing.[116]

SC-natalizumab offers the potential to reduce the impact of time and healthcare costs for people with MS,[117] with a recent trend toward patient and medical staff preference for the SC formulation, largely due to its convenience and time-saving benefits.[110] The different formulations can offer pros and cons depending on the individual, and given the preference-sensitive nature of treatment choice, the decision between IV and SC administration should be made through shared decision-making between the person with MS and their HCP.[110]

Early use. DMTs are more effective when the inflammatory stage is prominent, such as in early disease.[118] In highly active MS, HETs such as natalizumab and ocrelizumab are needed early in the disease course to inhibit inflammation and prevent disability accrual resulting from multiple relapses.[118] Several studies have demonstrated the benefit of early use of natalizumab. A retrospective study of DMT-naïve people showed that early initiation of natalizumab was associated with a significantly reduced relapse rate and lower risk of confirmed disability worsening compared to a first-line treatment with a lower-efficacy DMT (Figure 1(b)).[40] Another retrospective study, including 281 people with highly active MS starting HET with either natalizumab or ocrelizumab as first-line therapy within 1 year of diagnosis, found that the probability of achieving NEDA-3 was 66% with ocrelizumab and 68% with natalizumab.[118] Additionally, a cross-sectional study from Argentina reported that people with MS starting HET, including natalizumab, early in the disease course had a significantly lower burden of treatment and higher QoL than people receiving escalation therapy.[119] In an Austrian observational cohort study, 743 treatment-naïve people who started early intensive treatment, including 283 people receiving natalizumab, had decreased probability of relapse and EDSS progression compared with those who were treated with an escalation approach.[120] Furthermore, research into the potential benefits of very early use of natalizumab is ongoing with the AttackMS clinical trial, which is investigating the safety and efficacy of initiating natalizumab treatment within 14 days of MS symptom onset (ClinicalTrials.gov identifier: NCT05418010).

Switching to natalizumab from lower-efficacy therapies or other HETs. The ECTRIMS/EAN guidelines for the treatment of MS recommend switching people treated with IFN or glatiramer acetate who show evidence of disease activity to a more efficacious drug, with studies demonstrating benefit in switching to alemtuzumab, fingolimod, or natalizumab.[3] A real-world study of 2000 people with RRMS from the MSBase registry found that people demonstrated better outcomes in relapse rate and disability improvement with natalizumab than with fingolimod when switching from lower-efficacy DMTs.[121] Another real-world study using data from the MSBase registry compared the effectiveness of switching to ocrelizumab, cladribine, or natalizumab in 1045 people with RRMS who had previously been taking fingolimod and found that after fingolimod cessation, ocrelizumab and natalizumab were more effective in reducing relapses than cladribine.[122] Furthermore, in the authors' opinion, a switch to natalizumab may be appropriate for people receiving anti-CD20 therapies who have an increased incidence of infection.

Vaccination and bridging therapy. Immunosuppressive therapy for MS, particularly anti-CD20 therapies that exert their effects via lymphocyte depletion, may compromise the desired immune response of vaccination.[123] Consequently, clinicians are faced with a choice to either delay treatment with these agents until vaccination schedules are completed and risk adversely affecting MS prognosis or to rapidly start anti-CD20 therapy without prior vaccination, which could potentially expose people to severe, vaccine-preventable infections.[123] Furthermore, unlike natalizumab, treatments that cause long-term B-cell depletion are associated with severe side effects such as hypogammaglobulinemia and infections. However, for ocrelizumab, this may be mitigated by extended interval dosing.[124]

Results of a cohort study suggest that immunization with inactivated vaccines against hepatitis A, hepatitis B, and mRNA COVID-19 is safe and immunogenic in people with highly active MS receiving treatment with natalizumab.[123] Other studies have found that natalizumab treatment did not affect immunization with influenza or tetanus vaccines.[125] In contrast, while people treated with B-cell depleting ocrelizumab can mount an attenuated humoral response to inactivated vaccines,[126] available data indicate these

people have a reduced humoral response to SARS-CoV-2 vaccines.[127]

Regarding live vaccines, while generally not recommended for those on immunosuppressive/immunomodulating therapies, recent reports have shown that for people with MS treated with natalizumab, vaccination against varicella-zoster virus in people with highly active MS was not associated with AEs or increased disease activity,[128] and vaccination against yellow fever was not associated with worsening of MS disease activity or relapse rate in French and Swiss populations, respectively.[129,130] However, there is one report of vaccine-associated measles in a person with MS treated with natalizumab.[131]

For people with highly active MS who require both immunization and HET, natalizumab treatment may be used as a bridging therapy for a short-term period (3–6 months) while vaccination schedules have been completed, in order to prevent treatment delays.[123] Both the rapid onset of action and the reversibility of natalizumab treatment may make it suitable for use as a bridging therapy; however, this should be done with caution as a short exposure to natalizumab with a gap before redosing has been associated with higher incidences of anti-natalizumab antibodies and hypersensitivity reactions.[132] Nonetheless, the use of natalizumab during vaccination is supported by a study which demonstrated that switching DMTs from sphingosine 1-phosphate receptor modulators to natalizumab to restore lymphocyte counts prior to SARS-CoV-2 mRNA vaccination may result in a robust immune response after vaccination and avoid the risk of relapse associated with DMT interruption.[133]

Use of natalizumab in specific populations
Pregnancy and breastfeeding. Treating pregnant women with RRMS needs careful consideration of the risks and benefits to maternal and fetal health.[134] The natalizumab U.S. FDA prescribing information recommends use during pregnancy only if the potential benefit justifies the potential risk to the fetus,[43] while the natalizumab EMA summary of product characteristics recommends that discontinuation should be considered if a woman becomes pregnant while taking natalizumab, following a risk/benefit evaluation.[9,44] However, due to the risk of reactivation or rebound of disease activity upon cessation of natalizumab treatment, there is a rationale for continuing natalizumab at least until pregnancy is confirmed, or even during pregnancy in people with higher disease activity, as antibodies, including natalizumab, only minimally cross the placenta during the first trimester.[125]

An observational cohort study including 350 pregnant women with MS exposed to natalizumab, who either stopped treatment during their first trimester or continued beyond, showed that maintaining treatment beyond the first trimester may protect against disability worsening; although there was a higher fetal risk for hematological abnormalities, most did not need treatment.[134] Additionally, an Italian study of 170 pregnancies found that in women with MS treated with natalizumab before conception, continuation of natalizumab throughout pregnancy and its early resumption after delivery mitigated the risk of clinical and radiological disease reactivation and that this approach had no major impact on newborns' outcomes.[135]

Recently, a Delphi consensus panel reached agreement that when pregnancy is planned in people with high MS disease activity, in selected cases, either immune reconstitution therapy or natalizumab should be used.[136] Furthermore, consensus was reached that natalizumab during pregnancy should be continued in people with highly active disease,[136] given the risk of rebound disease activity with natalizumab discontinuation.[137] For people with historically highly active disease who decide to continue natalizumab during pregnancy, it may be beneficial to extend the dosing interval to every 6–8 weeks until 34-week gestation, but it should not be continued after this point.[137,138] Following delivery, it is recommended to resume natalizumab treatment in the first 4 weeks after birth to minimize the risk of return of disease activity.[138]

More data are needed on breastfeeding while undergoing treatment with natalizumab; however, it has been shown that natalizumab transfer to human breast milk is low, with a mean relative infant dose (a metric comparing the infant with maternal drug exposure) of 0.04% (standard deviation 0.03), which is far below the 10% threshold of concern for this metric.[139] Interdisciplinary care is vital for people with MS who are pregnant and/or breastfeeding; MS teams should work closely with specialized obstetrics and neonatology teams

for off-label decisions, particularly if immunotherapy continues during pregnancy.[137]

Pediatric-onset MS. There is a need for early diagnosis and treatment of MS in children, as, although the incidence and prevalence of MS is lower for children than for adults, it is the most common cause of non-traumatic neurological disability in young adults.[140] Furthermore, pediatric-onset MS also has a higher relapse rate than adult-onset MS, which is thought to relate to a more inflammatory disease course in pediatric MS.[141] Historically, initiation of IFN beta or glatiramer acetate was recommended, with the use of HET reserved for people with more active disease.[142] While there are no recent and specific guidelines for the treatment of pediatric-onset MS, there is increasing evidence for a strong effect of HET on reducing relapse rate, disability, and MRI activity in this population, and as such, early use of HET has been suggested as a new therapeutic approach for children with MS.[142]

Several studies have demonstrated the safety and efficacy of natalizumab in pediatric-onset MS, with more real-world data available on natalizumab in this population than for anti-CD20 therapies.[142] A post-marketing meta-analysis conducted using data from 621 children with MS treated with natalizumab, 158 of whom had data available prior to treatment, demonstrated a reduction in ARR during treatment.[44] A small Spanish study of nine children with MS found that safety and efficacy of natalizumab in children was in line with the experience published in adult populations.[143] Another study of 101 children with MS from an Italian cohort found that natalizumab was well tolerated, and efficacious in most cases.[144] The TyPed study, which included 21 children with MS treated with natalizumab in Portugal, also demonstrated that natalizumab may be an effective and well-tolerated DMT for pediatric MS, with results in line with the adult population.[145] Furthermore, a retrospective study evaluating the efficacy and safety of natalizumab in both adults and children with MS found that clinical and radiological outcomes were similar in both populations, with fewer PIRA events observed in children with MS compared with adults.[146] Taken together, these data support the potential use of natalizumab as a well-tolerated and effective treatment for pediatric-onset MS.

Only a few reports of PML exist in the pediatric population with MS.[147] As PML is the result of reactivation of a primary, usually asymptomatic infection with the JC virus, children may be at lower risk for this condition, as long as JC virus infection has not yet occurred.[147] Another reason may be that the number of children with MS treated with natalizumab is possibly too low to draw any significant risk estimates, as the safety and efficacy of natalizumab in children and adolescents has not been established.[145]

Comorbidities. Comorbidities are common in people with MS and are associated with higher relapse rates, greater physical and cognitive impairments, lower HRQoL, and increased mortality.[148] Autoimmune comorbidities may pose particular challenges for people with MS, especially when a DMT does not successfully treat both the MS and the comorbid disease, or may even exacerbate the latter, as seen with psoriasis.[149] However, natalizumab may be a viable treatment option. In a retrospective analysis of 18 people with MS and comorbid psoriasis, who were switched from other DMTs due to lack of treatment efficacy for MS or worsening or development of psoriasis, improvement in both MS and psoriasis was observed after switching to natalizumab from other DMTs.[149]

Another autoimmune disease that shares comorbidity with MS is inflammatory bowel disease, including Crohn's disease and ulcerative colitis, due to their common epidemiological and immunological patterns.[150,151] In the U.S., natalizumab is indicated for the treatment of Crohn's disease as well as MS, so it could be used to treat individuals with both conditions.[43] People with Crohn's disease have shown improvements in randomized controlled trials.[152,153]

A comorbidity that can complicate treatment decisions in MS is liver disease due to the risk of drug-induced liver injury.[154] However, a case report has described natalizumab with ursodeoxycholic acid as being used successfully in a person with comorbid progressive familial intrahepatic cholestasis type-3 after other DMTs were tried and associated with drug-induced liver injury.[154]

Cardiovascular comorbidities are associated with the risk of MS progression. An observational,

prospective cohort study in people with RRMS suggested that natalizumab treatment had a beneficial effect on lipid profile and increased uric acid levels during 12.9 ± 6.2 months of treatment; subsequent association with disease outcomes is unknown but of interest,[155] though increased uric acid levels have previously been associated with reduced risk of relapse and disease disability.[156] Taken together, natalizumab is approved as an effective treatment for MS and Crohn's disease and may show beneficial effects in people with MS who have other comorbidities.

What have we learned from natalizumab and what does the future hold?

As the first monoclonal antibody to be approved for the treatment of MS, 20 years of natalizumab use has brought much to the MS community.[1] It has a unique mode of action[6] that, although likely to contribute to the increased risk of PML,[88] is also responsible for its efficacy and unique properties of rapid onset of action and reversibility, the latter of which avoids long-term immunosuppression.[57,64] These properties, and natalizumab's attractive overall risk/benefit profile, may make it an option for people who are complex to treat, including those in need of rapid onset of treatment effects, those who are pregnant or breastfeeding, children with MS, and people with MS with comorbidities. Over 20 years of experience with natalizumab has not only increased our understanding of the different MS treatment strategies involving the use of this agent and the types of people that are likely to derive the most benefit, but it also increased our understanding of the immunology of the disease itself, along with some of the first robust risk management strategies in MS. As the diagnostic criteria for MS evolves to improve early diagnosis, early use of HET, including natalizumab, will become increasingly important in managing the disease.

The definition of "rapidly evolving severe MS" resulted from post hoc analyses of large clinical trials to identify people who might benefit from early treatment with moderately high-efficacy drugs or HET.[157] As well as the introduction of a new therapeutic strategy for the treatment of MS, the modulation of immune cell trafficking across the BBB is an example of reverse translational medicine.[158] Data from clinical trials of natalizumab and fingolimod have revealed the involvement of different compartments in relapsing versus non-relapsing MS immune biology and contributed to our understanding of CNS immune surveillance.[158]

In addition to paving the way for new therapeutic approaches for the management of MS as the first high-efficacy monoclonal antibody therapy,[159] natalizumab was also "ahead of the curve" in terms of the management of AEs. The risk of PML associated with natalizumab led to the development of the first structured risk management plan in MS treatment, allowing for individualization and risk stratification, which has been successful in reducing the incidence of PML over time.[8,95] Looking forward, further progress is expected in understanding why some at-risk people do not develop PML, particularly the role of genetics in individual PML risk.[160]

Finally, natalizumab may have potential in other indications beyond MS. For example, natalizumab has been tested as a treatment for metastatic osteosarcoma (ClinicalTrials.gov ID NCT03811886). As metastatic cancers use the VLA-4–VCAM-1 interaction to spread to the lung and other sites, anti-α4 integrin inhibitors, such as natalizumab, may reduce the risk of these cancers spreading.[161] Moreover, in the authors' opinion, natalizumab may have the potential to treat CNS complications associated with cancer immunotherapies. First, checkpoint inhibitors can be associated with neurological immune-related AEs due to upregulated activity of the immune system, where these people are generally responsive to immune-modulating therapy.[162] Second, chimeric antigen receptor (CAR) T-cell therapy can result in immune effector cell-associated neurotoxicity syndrome due to the diffusion of cytokines and transmigration of CAR T cells, endogenous T cells, and monocytes into the cerebrospinal fluid and CNS.[163] In addition, the authors also suggest that natalizumab may have application in other CNS complications such as tuberculosis meningitis, which is underpinned by BBB dysfunction and the influx of leukocytes into the CNS.[164] Taken together, there is the potential to bring 20 years of experience with natalizumab in MS to new therapy areas.

Declarations

Ethics approval and consent to participate
Not applicable.

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References

1. Barnes K. The first monoclonal antibody therapy, https://www.nature.com/articles/d42859-018-00024-6 (2018, accessed 13 February 2025).

2. Pardo G and Jones DE. The sequence of disease-modifying therapies in relapsing multiple sclerosis: safety and immunologic considerations. *J Neurol* 2017; 264: 2351–2374.

3. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Eur J Neurol* 2018; 25: 215–237.

4. Butzkueven H, Kappos L, Wiendl H, et al. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). *J Neurol Neurosurg Psychiatry* 2020; 91: 660–668.

5. Fernández O, Oreja-Guevara C, Arroyo R, et al. Natalizumab treatment of multiple sclerosis in Spain: results of an extensive observational study. *J Neurol* 2012; 259: 1814–1823.

6. Yang JH, Rempe T, Whitmire N, et al. Therapeutic advances in multiple sclerosis. *Front Neurol* 2022; 13: 824926.

7. Planas R, Martin R and Sospedra M. Long-term safety and efficacy of natalizumab in relapsing-remitting multiple sclerosis: impact on quality of life. *Patient Relat Outcome Meas* 2014; 5: 25–33.

8. Vukusic S, Rollot F, Casey R, et al. Progressive multifocal leukoencephalopathy incidence and risk stratification among natalizumab users in France. *JAMA Neurol* 2020; 77: 94–102.

9. European Medicines Agency. Tyruko summary of product characteristics, https://www.ema.europa.eu/en/documents/product-information/tyruko-epar-product-information_en.pdf (2023, accessed 13 February 2025).

10. US Food and Drug Administration. Tyruko (natalizumab-sztn) injection, for intravenous use, full prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761322s000lbl.pdf (2023, accessed 13 February 2025).

11. Selmaj K, Roth K, Hofler J, et al. Introducing the biosimilar paradigm to neurology: the totality of evidence for the first biosimilar natalizumab. *BioDrugs* 2024; 38: 755–767.

12. Li E, Goh A, Gupta S, et al. Budget impact analysis of biosimilar natalizumab in the US. *Am J Manag Care* 2024; 30: e191–e197.

13. Hutchinson M. Natalizumab: a new treatment for relapsing remitting multiple sclerosis. *Ther Clin Risk Manag* 2007; 3: 259–268.

14. Filippi M, Bar-Or A, Piehl F, et al. Multiple sclerosis. *Nat Rev Dis Primers* 2018; 4: 43.

15. Charabati M, Wheeler MA, Weiner HL, et al. Multiple sclerosis: neuroimmune crosstalk and therapeutic targeting. *Cell* 2023; 186: 1309–1327.

16. Younger DS. Multiple sclerosis: motor dysfunction. *Handb Clin Neurol* 2023; 196: 119–147.

17. Scherder RJ, Kant N, Wolf ET, et al. Sensory function and chronic pain in multiple sclerosis. *Pain Res Manag* 2018; 2018: 1924174.

18. Serra A, Chisari CG and Matta M. Eye movement abnormalities in multiple sclerosis: pathogenesis, modeling, and treatment. *Front Neurol* 2018; 9: 31.

19. Merson RM and Rolnick MI. Speech-language pathology and dysphagia in multiple sclerosis. *Phys Med Rehabil Clin N Am* 1998; 9: 631–641.

20. Preziosi G, Gordon-Dixon A and Emmanuel A. Neurogenic bowel dysfunction in patients with multiple sclerosis: prevalence, impact, and management strategies. *Degener Neurol Neuromuscul Dis* 2018; 8: 79–90.

21. Tornic J and Panicker JN. The management of lower urinary tract dysfunction in multiple sclerosis. *Curr Neurol Neurosci Rep* 2018; 18: 54.

22. Haki M, Al-Biati HA, Al-Tameemi ZS, et al. Review of multiple sclerosis: epidemiology, etiology, pathophysiology, and treatment. *Medicine (Baltimore)* 2024; 103: e37297.

23. Alroughani R and Boyko A. Pediatric multiple sclerosis: a review. *BMC Neurol* 2018; 18: 27.

24. Multiple Sclerosis News Today. ECTRIMS2024: McDonald criteria changes could speed diagnoses, https://multiplesclerosisnewstoday.com/news-posts/2024/09/25/ectrims-2024-mcdonald-criteria-changes-speed-diagnoses/ (2024, accessed 22 January 2025).

25. Klineova S and Lublin FD. Clinical course of multiple sclerosis. *Cold Spring Harb Perspect Med* 2018; 8: a028928.

26. Kappos L, Wolinsky JS, Giovannoni G, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol* 2020; 77: 1132–1140.

27. Lublin FD, Häring DA, Ganjgahi H, et al. How patients with multiple sclerosis acquire disability. *Brain* 2022; 145: 3147–3161.

28. Tsantes E, Curti E, Collura F, et al. Five- and seven-year prognostic value of new effectiveness measures (NEDA, MEDA and six-month delayed NEDA) in relapsing-remitting multiple sclerosis. *J Neurol Sci* 2020; 414: 116827.

29. Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *Lancet Neurol* 2009; 8: 254–260.

30. Amin M and Hersh CM. Updates and advances in multiple sclerosis neurotherapeutics. *Neurodegener Dis Manag* 2023; 13: 47–70.

31. Multiple Sclerosis Association of America. The FDA-approved long-term treatments for MS, https://mymsaa.org/ms-information/treatments/long-term/ (2025, accessed 22 January 2025).

32. MS Society. Disease-modifying therapies, https://www.mssociety.org.uk/living-with-ms/treatments-and-therapies/disease-modifying-therapies (2022, accessed 22 January 2025).

33. Piehl F. Current and emerging disease-modulatory therapies and treatment targets for multiple sclerosis. *J Intern Med* 2021; 289: 771–791.

34. Stankiewicz JM and Weiner HL. An argument for broad use of high efficacy treatments in early multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2019; 7: e636.

35. Casanova B, Quintanilla-Bordás C and Gascón F. Escalation vs. early intense therapy in multiple sclerosis. *J Pers Med* 2022; 12: 119.

36. Ziemssen T, Derfuss T, de Stefano N, et al. Optimizing treatment success in multiple sclerosis. *J Neurol* 2016; 263: 1053–1065.

37. Spelman T, Magyari M, Piehl F, et al. Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis: data from 2 different national strategies. *JAMA Neurol* 2021; 78: 1197–1204.

38. He A, Merkel B, Brown JWL, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol* 2020; 19: 307–316.

39. Simpson A, Mowry EM and Newsome SD. Early aggressive treatment approaches for multiple sclerosis. *Curr Treat Options Neurol* 2021; 23: 19.

40. Butzkueven H, Kalincik T, Patti F, et al. Long-term clinical outcomes in patients with multiple sclerosis who are initiating disease-modifying therapy with natalizumab compared with BRACETD first-line therapies. *Ther Adv Neurol Disord* 2024; 17: 17562864231221331.

41. Giovannoni G, Marta M, Davis A, et al. Switching patients at high risk of PML from natalizumab to another disease-modifying therapy. *Pract Neurol* 2016; 16: 389–393.

42. Sheremata WA, Minagar A, Alexander JS, et al. The role of alpha-4 integrin in the aetiology of multiple sclerosis: current knowledge and therapeutic implications. *CNS Drugs* 2005; 19: 909–922.

43. US Food and Drug Administration. Tysabri (natalizumab) injection full prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125104s0576lbl.pdf (2004, accessed 13 February 2025).

44. European Medicines Agency. Tysabri summary of product characteristics, https://www.ema.europa.eu/en/documents/product-information/tysabri-epar-product-information_en.pdf (2006, accessed 13 February 2025).

45. World Health Organization. WHO expert committee on biological standardization. Annex 2. Guidelines on evaluation of similar biotherapeutic products (SBPs), https://cdn.who.int/media/docs/default-source/biologicals/trs_977_annex_2.pdf?sfvrsn=e2389a69_3 (2013, accessed 13 February 2025).

46. Rudick RA and Sandrock A. Natalizumab: alpha 4-integrin antagonist selective adhesion molecule inhibitors for MS. *Expert Rev Neurother* 2004; 4: 571–580.

47. Tubridy N, Behan PO, Capildeo R, et al. The effect of anti-alpha4 integrin antibody on brain lesion activity in MS. The UK Antegren Study Group. *Neurology* 1999; 53: 466–472.

48. Bayless KJ, Meininger GA, Scholtz JM, et al. Osteopontin is a ligand for the alpha4beta1 integrin. *J Cell Sci* 1998; 111(Pt 9): 1165–1174.

49. Tchilian EZ, Owen JJT and Jenkinson EJ. Anti-alpha 4 integrin antibody induces apoptosis in murine thymocytes and staphylococcal enterotoxin B-activated lymph node T cells. *Immunology* 1997; 92: 321–327.

50. Sucksdorff M, Tuisku J, Matilainen M, et al. Natalizumab treatment reduces microglial activation in the white matter of the MS brain. *Neurol Neuroimmunol Neuroinflamm* 2019; 6: e574.

51. Ramos-Cejudo J, Oreja-Guevara C, Stark Aroeira L, et al. Treatment with natalizumab in relapsing-remitting multiple sclerosis patients induces changes in inflammatory mechanism. *J Clin Immunol* 2011; 31: 623–631.

52. Liampas A, Tseriotis V-S, Mavridis T, et al. Effects of natalizumab on oligoclonal bands in the cerebrospinal fluid of patients with multiple sclerosis: a systematic review and meta-analysis. *Neurol Sci* 2025; 46: 1541–1553.

53. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 899–910.

54. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 911–923.

55. Morrow SA, Clift F, Devonshire V, et al. Use of natalizumab in persons with multiple sclerosis: 2022 update. *Mult Scler Relat Disord* 2022; 65: 103995.

56. O'Connor PW, Goodman A, Willmer-Hulme AJ, et al. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. *Neurology* 2004; 62: 2038–2043.

57. Kappos L, O'Connor PW, Polman CH, et al. Clinical effects of natalizumab on multiple sclerosis appear early in treatment course. *J Neurol* 2013; 260: 1388–1395.

58. Butzkueven H, Licata S, Jeffery D, et al. Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study. *BMJ Open* 2020; 10: e038861.

59. Hersh CM, Pang M, Miller DM, et al. Comparison of time to clinically meaningful improvement in quality of life in neurological disorders in patients treated with natalizumab versus ocrelizumab. *Neurodegener Dis Manag* 2024; 14: 21–33.

60. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017; 376: 209–220.

61. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med* 2020; 383: 546–557.

62. Bar-Or A, Wiendl H, Montalban X, et al. Rapid and sustained B-cell depletion with subcutaneous ofatumumab in relapsing multiple sclerosis: APLIOS, a randomized phase-2 study. *Mult Scler* 2022; 28: 910–924.

63. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008; 358: 676–688.

64. Plavina T, Muralidharan KK, Kuesters G, et al. Reversibility of the effects of natalizumab on peripheral immune cell dynamics in MS patients. *Neurology* 2017; 89: 1584–1593.

65. Derfuss T, Mehling M, Papadopoulou A, et al. Advances in oral immunomodulating therapies in relapsing multiple sclerosis. *Lancet Neurol* 2020; 19: 336–347.

66. Monschein T, Dekany S, Zrzavy T, et al. Real-world use of natalizumab in Austria: data from the Austrian Multiple Sclerosis Treatment Registry (AMSTR). *J Neurol* 2023; 270: 3779–3786.

67. Cree BAC, Cohen JA, Reder AT, et al. Disability improvement as a clinically relevant outcome in clinical trials of relapsing forms of multiple sclerosis. *Mult Scler* 2021; 27: 2219–2231.

68. Phillips JT, Giovannoni G, Lublin FD, et al. Sustained improvement in Expanded Disability Status Scale as a new efficacy measure of neurological change in multiple sclerosis: treatment effects with natalizumab in patients with relapsing multiple sclerosis. *Mult Scler* 2011; 17: 970–979.

69. Wiendl H, Spelman T, Butzkueven H, et al. Real-world disability improvement in patients with relapsing-remitting multiple sclerosis treated with natalizumab in the Tysabri Observational Program. *Mult Scler* 2021; 27: 719–728.

70. Buron MD, Christensen JR, Pontieri L, et al. Natalizumab treatment of multiple sclerosis—a Danish nationwide study with 13 years of follow-up. *Mult Scler Relat Disord* 2023; 74: 104713.

71. Dalton CM, Miszkiel KA, Barker GJ, et al. Effect of natalizumab on conversion of gadolinium enhancing lesions to T1 hypointense lesions in relapsing multiple sclerosis. *J Neurol* 2004; 251: 407–413.

72. Gunnarsson M, Malmeström C, Axelsson M, et al. Axonal damage in relapsing multiple sclerosis is markedly reduced by natalizumab. *Ann Neurol* 2010; 69: 83–89.

73. Planche V, Moisset X, Morello R, et al. Improvement of quality of life and its relationship with neuropsychiatric outcomes in patients with multiple sclerosis starting treatment with natalizumab: a 3-year follow-up multicentric study. *J Neurol Sci* 2017; 382: 148–154.

74. Rudick RA, Miller D, Hass S, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol* 2007; 62: 335–346.

75. Perumal J, Balabanov R, Su R, et al. Improvements in cognitive processing speed, disability, and patient-reported outcomes in patients with early relapsing-remitting multiple sclerosis treated with natalizumab: results of a 4-year, real-world, open-label study. *CNS Drugs* 2022; 36: 977–993.

76. Stephenson JJ, Kern DM, Agarwal SS, et al. Impact of natalizumab on patient-reported outcomes in multiple sclerosis: a longitudinal study. *Health Qual Life Outcomes* 2012; 10: 155.

77. Penner IK, Sivertsdotter EC, Celius EG, et al. Improvement in fatigue during natalizumab treatment is linked to improvement in depression and day-time sleepiness. *Front Neurol* 2015; 6: 18.

78. Cohen M, Mondot L, Bucciarelli F, et al. BEST-MS: a prospective head-to-head comparative study of natalizumab and fingolimod in active relapsing MS. *Mult Scler* 2021; 27: 1556–1563.

79. Guerra T, Caputo F, Orlando B, et al. Long-term comparative analysis of no evidence of disease activity (NEDA-3) status between multiple sclerosis patients treated with natalizumab and fingolimod for up to 4 years. *Neurol Sci* 2021; 42: 4647–4655.

80. Rollot F, Couturier J, Casey R, et al. Comparative effectiveness of natalizumab versus anti-CD20 in highly active relapsing-remitting multiple sclerosis after fingolimod withdrawal. *Neurotherapeutics* 2022; 19: 476–490.

81. Roos I, Sharmin S, Malpas C, et al. Effectiveness of cladribine compared to fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis. *Mult Scler* 2024; 30: 1163–1175.

82. Haggiag S, Prosperini L, Galgani S, et al. Extratemporal herpes encephalitis during natalizumab treatment: a case report. *Mult Scler Relat Disord* 2016; 10: 134–136.

83. Kwiatkowski A, Gallois J, Bilbault N, et al. Herpes encephalitis during natalizumab treatment in multiple sclerosis. *Mult Scler* 2012; 18: 909–911.

84. Sharma K, Ballham SA, Inglis KEA, et al. Does natalizumab treatment increase the risk of herpes simplex encephalitis in multiple sclerosis? Case and discussion. *Mult Scler Relat Disord* 2013; 2: 385–387.

85. Ciano-Petersen NL, Aliaga-Gaspar P, Hurtado-Guerrero I, et al. Natalizumab-immunogenicity evaluation in patients with infusion related events or disease exacerbations. *Front Immunol* 2023; 14: 1242508.

86. Link J, Ramanujam R, Auer M, et al. Clinical practice of analysis of anti-drug antibodies against interferon beta and natalizumab in multiple sclerosis patients in Europe: a descriptive study of test results. *PLoS One* 2017; 12: e0170395.

87. Clerico M, Artusi CA, Di Liberto A, et al. Long-term safety evaluation of natalizumab for the treatment of multiple sclerosis. *Expert Opin Drug Saf* 2017; 16: 963–972.

88. Major EO, Yousry TA and 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.

89. Cortese I, Reich DS and Nath A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. *Nat Rev Neurol* 2021; 17: 37–51.

90. Vivekanandan G, Abubacker AP, Myneni R, et al. Risk of progressive multifocal leukoencephalopathy in multiple sclerosis patient treated with natalizumab: a systematic review. *Cureus* 2021; 13: e14764.

91. 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.

92. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. *Neurology* 2013; 80: 1430–1438.

93. Kelsey R. The risk of natalizumab-associated PML is revealed, https://www.nature.com/articles/d42859-018-00025-5 (2018, 20 February 2025).

94. US Food and Drug Administration. Tysabri (natalizumab) label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/125104s015LBL.pdf (2006, accessed 13 February 2025).

95. Kågström S, Fält A, Berglund A, et al. Reduction of the risk of PML in natalizumab treated MS patients in Sweden: an effect of improved PML risk surveillance. *Mult Scler Relat Disord* 2021; 50: 102842.

96. Biogen. PML risk estimates algorithm, https://biogenlinc.co.uk/products/ms-portfolio/tysabri/pml/ (2023, accessed 13 February 2025).

97. 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.

98. Giovannoni G. Barts-MS PML risk guide, https://msselfie.co.uk/dmts-safety/natalizumab-pml/attachment/barts-ms-pml-risk-guide-table-simplified_27-06-23/ (2023, accessed 13 February 2025).

99. Perncezky J and Sellner J. Natalizumab extended-interval dosing in multiple sclerosis to mitigate progressive multifocal leukoencephalopathy risk: initial study evidence and real-world experience. *J Cent Nerv Syst Dis* 2022; 14: 11795735221135485.

100. Ryerson LZ, Foley J, Chang I, et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. *Neurology* 2019; 93: e1452–e1462.

101. De Mercanti SF, Signori A, Cordioli C, et al. MRI activity and extended interval of natalizumab dosing regimen: a multicentre Italian study. *J Neurol Sci* 2021; 424: 117385.

102. Jeantin L, Boudot de la Motte M, Deschamps R, et al. Natalizumab extended-interval dosing in a real-life setting. *J Neurol Sci* 2023; 450: 120689.

103. Ryerson LZ, Foley JF, Defer G, et al. Exploratory clinical efficacy and patient-reported outcomes from NOVA: a randomized controlled study of intravenous natalizumab 6-week dosing versus continued 4-week dosing for relapsing-remitting multiple sclerosis. *Mult Scler Relat Disord* 2023; 72: 104561.

104. Johnsson M, Farman HH, Blennow K, et al. No increase of serum neurofilament light in relapsing-remitting multiple sclerosis patients switching from standard to extended-interval dosing of natalizumab. *Mult Scler* 2022; 28: 2070–2080.

105. Zanghì A, Gallo A, Avolio C, et al. Exit strategies in natalizumab-treated RRMS at high risk of progressive multifocal leukoencephalopathy: a multicentre comparison study. *Neurotherapeutics* 2021; 18: 1166–1174.

106. Salhofer-Polanyi S, Baumgartner A, Kraus J, et al. What to expect after natalizumab cessation in a real-life setting. *Acta Neurol Scand* 2014; 130: 97–102.

107. Hartung HP, Mares J, Meuth SG, et al. Multiple sclerosis: switching from natalizumab to other high-efficacy treatments to mitigate progressive multifocal leukoencephalopathy risk. *Neurotherapeutics* 2021; 18: 1654–1656.

108. Brown JD, Muston BT and Massey J. Switching from natalizumab to an anti-CD20 monoclonal antibody in relapsing remitting multiple sclerosis: a systematic review. *Mult Scler Relat Disord* 2024; 86: 105605.

109. Bigaut K, Kremer L, Fabacher T, et al. Ocrelizumab versus fingolimod after natalizumab cessation in multiple sclerosis: an observational study. *J Neurol* 2022; 269: 3295–3300.

110. Gold R, Schmidt S, Deisenhammer F, et al. Real-world evidence and patient preference for subcutaneous versus intravenous natalizumab in the treatment of relapsing-remitting multiple sclerosis—initial results from the observational SISTER study. *Ther Adv Neurol Disord* 2024; 17: 17562864241241382.

111. Trojano M, Ramió-Torrentà L, Grimaldi LM, et al. A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. *Mult Scler* 2021; 27: 2240–2253.

112. Plavina T, Fox EJ, Lucas N, et al. A randomized trial evaluating various administration routes of natalizumab in multiple sclerosis. *J Clin Pharmacol* 2016; 56: 1254–1262.

113. Mariottini A, Mealli F, Mattei A, et al. Comparative efficacy of subcutaneous versus intravenous natalizumab on annualized relapse rate: a post-hoc analysis of the REFINE study. *Mult Scler Relat Disord* 2024; 91: 105852.

114. Gelissen LMY, Loveless S, Toorop AA, et al. Subcutaneous administration of natalizumab can lead to lower drug concentrations compared to intravenous administration. *Mult Scler Relat Disord* 2024; 90: 105796.

115. Toorop AA, van Kempen ZLE, Steenhuis M, et al. Decrease of natalizumab drug levels after switching from intravenous to subcutaneous administration in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2023; 94: 482–486.

116. Ruggieri S, Ianniello A, Copetti M, et al. Treatment modifiers across different regimens of natalizumab treatment in MS: an Italian real-world experience. *Neurotherapeutics* 2024; 21: e00338.

117. Filippi M, Grimaldi L, Conte A, et al. Intravenous or subcutaneous natalizumab in patients with relapsing-remitting multiple sclerosis: investigation on efficiency and savings—the EASIER study. *J Neurol* 2024; 271: 340–354.

118. Signoriello E, Signori A, Lus G, et al. NEDA-3 achievement in early highly active relapsing remitting multiple sclerosis patients treated with ocrelizumab or natalizumab. *Mult Scler Relat Disord* 2024; 87: 105594.

119. Rojas JI, Carnero Contentti E, Alonso R, et al. Burden of treatment and quality of life in relapsing remitting multiple sclerosis patients under early high efficacy therapy in Argentina: data from the Argentinean registry. *Mult Scler Relat Disord* 2024; 85: 105543.

120. Guger M, Enzinger C, Leutmezer F, et al. Early intensive versus escalation treatment in patients with relapsing-remitting multiple sclerosis in Austria. *J Neurol* 2024; 271: 3142–3152.

121. Spelman T, Horakova D, Ozakbas S, et al. Switching to natalizumab or fingolimod in multiple sclerosis: comparative effectiveness and effect of pre-switch disease activity. *Mult Scler Relat Disord* 2023; 70: 104477.

122. Zhu C, Zhou Z, Roos I, et al. Comparing switch to ocrelizumab, cladribine or natalizumab after fingolimod treatment cessation in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2022; 93: 1330–1337.

123. Carvajal R, Zabalza A, Carbonell-Mirabent P, et al. Vaccine safety and immunogenicity in patients with multiple sclerosis treated with natalizumab. *JAMA Netw Open* 2024; 7: e246345.

124. Schuckmann A, Steffen F, Zipp F, et al. Impact of extended interval dosing of ocrelizumab on immunoglobulin levels in multiple sclerosis. *Med* 2023; 4: 361–372.e363.

125. Krajnc N, Bsteh G, Berger T, et al. Monoclonal antibodies in the treatment of relapsing multiple sclerosis: an overview with emphasis on pregnancy, vaccination, and risk management. *Neurotherapeutics* 2022; 19: 753–773.

126. Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. *Neurology* 2020; 95: e1999–e2008.

127. Sormani MP, Inglese M, Schiavetti I, et al. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. *EBioMedicine* 2021; 72: 103581.

128. Paybast S, Nahayati MA, Shahmohammadi S, et al. Is it time to consider the live attenuated

varicella-zoster virus (VZV) vaccination safe in patients with multiple sclerosis treated with natalizumab? An extension study of the first Iranian experience. *Mult Scler Relat Disord* 2025; 95: 106285.

129. Huttner A, Eperon G, Lascano AM, et al. Risk of MS relapse after yellow fever vaccination: a self-controlled case series. *Neurol Neuroimmunol Neuroinflamm* 2020; 7: e726.

130. Papeix C, Mazoyer J, Maillart E, et al. Multiple sclerosis: is there a risk of worsening after yellow fever vaccination? *Mult Scler* 2021; 27: 2280–2283.

131. Miauton A, Tan R, Pantazou V, et al. Vaccine-associated measles in a patient treated with natalizumab: a case report. *BMC Infect Dis* 2020; 20: 753.

132. O'Connor P, Goodman A, Kappos L, et al. Long-term safety and effectiveness of natalizumab redosing and treatment in the STRATA MS study. *Neurology* 2014; 83: 78–86.

133. Kanakura M, Kihara K, Kinoshita M, et al. Switching disease-modifying therapies from sphingosine-1-phosphate receptor modulators to natalizumab or dimethyl fumarate restores immune responses after SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis. *Clin Neurol Neurosurg* 2024; 243: 108378.

134. Thiel S, Litvin N, Haben S, et al. Disease activity and neonatal outcomes after exposure to natalizumab throughout pregnancy. *J Neurol Neurosurg Psychiatry* 2024; 95: 561–570.

135. 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.

136. Oreja-Guevara C, Tintoré M, Meca V, et al. Family planning in fertile-age patients with multiple sclerosis (MS) (ConPlanEM Study): Delphi consensus statements. *Cureus* 2023; 15: e44056.

137. Graber M, Panchaud A, Legardeur H, et al. Recommendations for the treatment of multiple sclerosis in family planning, pregnancy and lactation in Switzerland: immunotherapy. *Clin Transl Neurosci* 2024; 8: 26.

138. O'Leary S, Brugger HT, Wallentine D, et al. Practical clinical guidelines for natalizumab treatment in patients with relapsing multiple sclerosis. *J Infus Nurs* 2023; 46: 347–359.

139. Proschmann U, Haase R, Inojosa H, et al. Drug and neurofilament levels in serum and breastmilk of women with multiple sclerosis exposed to natalizumab during pregnancy and lactation. *Front Immunol* 2021; 12: 715195.

140. de Chalus A, Taveira M and Deiva K. Pediatric onset multiple sclerosis: future challenge for early diagnosis and treatment. *Presse Med* 2021; 50: 104069.

141. Gorman MP, Healy BC, Polgar-Turcsanyi M, et al. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. *Arch Neurol* 2009; 66: 54–59.

142. Ghezzi A. Old and new strategies in the treatment of pediatric multiple sclerosis: a personal view for a new treatment approach. *Neurol Ther* 2024; 13: 949–963.

143. Arnal-Garcia C, García-Montero MR, Málaga I, et al. Natalizumab use in pediatric patients with relapsing-remitting multiple sclerosis. *Eur J Paediatr Neurol* 2013; 17: 50–54.

144. Ghezzi A, Moiola L, Pozzilli C, et al. Natalizumab in the pediatric MS population: results of the Italian registry. *BMC Neurol* 2015; 15: 174.

145. Palavra F, Figueiroa S, Correia AS, et al. TyPed study: natalizumab for the treatment of pediatric-onset multiple sclerosis in Portugal. *Mult Scler Relat Disord* 2021; 51: 102865.

146. Puthenparampil M, Gaggiola M, Ponzano M, et al. High NEDA and no PIRA in natalizumab-treated patients with pediatric-onset multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2024; 11: e200303.

147. Yeh EA and Weinstock-Guttman B. Natalizumab in pediatric multiple sclerosis patients. *Ther Adv Neurol Disord* 2010; 3: 293–299.

148. Marrie RA, Fisk JD, Fitzgerald K, et al. Etiology, effects and management of comorbidities in multiple sclerosis: recent advances. *Front Immunol* 2023; 14: 1197195.

149. Berkovich R, Yakupova A, Eskenazi J, et al. Improvement of comorbid psoriasis in patients with MS treated with natalizumab. *Neurol Neuroimmunol Neuroinflamm* 2021; 8: e961.

150. Kosmidou M, Katsanos AH, Katsanos KH, et al. Multiple sclerosis and inflammatory bowel diseases: a systematic review and meta-analysis. *J Neurol* 2017; 264: 254–259.

151. Wang X, Wan J, Wang M, et al. Multiple sclerosis and inflammatory bowel disease: a

systematic review and meta-analysis. *Ann Clin Transl Neurol* 2022; 9: 132–140.

152. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. *N Engl J Med* 2003; 348: 24–32.

153. Nelson SML, TM Nguyen, McDonald JWD, et al. Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2018; 8: CD006097.

154. De Masi R, Orlando S and De Donno A. Progressive familial intrahepatic cholestasis type-3 and multiple sclerosis: lessons from comorbidity. *Ann Clin Transl Neurol* 2019; 6: 2347–2350.

155. Moccia M, Albero R, Lanzillo R, et al. Cardiovascular profile improvement during natalizumab treatment. *Metab Brain Dis* 2018; 33: 981–986.

156. Moccia M, Lanzillo R, Costabile T, et al. Uric acid in relapsing-remitting multiple sclerosis: a 2-year longitudinal study. *J Neurol* 2015; 262: 961–967.

157. Fernández Ó. Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? *Mult Scler Relat Disord* 2017; 17: 75–83.

158. Schwab N and Wiendl H. Learning CNS immunopathology from therapeutic interventions. *Sci Transl Med* 2023; 15: eadg7863.

159. Cree BAC, Oksenberg JR and Hauser SL. Multiple sclerosis: two decades of progress. *Lancet Neurol* 2022; 21: 211–214.

160. Hatchwell E, Smith EB 3rd, Jalilzadeh S, et al. Progressive multifocal leukoencephalopathy genetic risk variants for pharmacovigilance of immunosuppressant therapies. *Front Neurol* 2022; 13: 1016377.

161. Chen Q and Massague J. Molecular pathways: VCAM-1 as a potential therapeutic target in metastasis. *Clin Cancer Res* 2012; 18: 5520–5525.

162. Fan S, Ren H, Zhao L, et al. Neurological immune-related adverse events associated with immune checkpoint inhibitors: a review of the literature. *Asia Pac J Clin Oncol* 2020; 16: 291–298.

163. Morris EC, Neelapu SS, Giavridis T, et al. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol* 2022; 22: 85–96.

164. Barnacle JR, Davis AG and Wilkinson RJ. Recent advances in understanding the human host immune response in tuberculous meningitis. *Front Immunol* 2024; 14: 1326651.