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NATALIZUMAB IN MULTIPLE SCLEROSIS – A REVIEW OF DIFFERENT DOSING REGIMENS, SIDE EFFECTS, COMPARISON WITH OTHER DISEASE-MODIFYING THERAPIES WITH ADDITIONAL ATTENTION TO USE IN PREGNANCY AND THE PEDIATRIC POPULATION

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ABSTRACT

Objective: The aim of this review was to evaluate the clinical efficacy, optimization of dosing regimens, safety profile, and socioeconomic aspects of natalizumab (NTZ) use in the treatment of multiple sclerosis (MS), with a additional focus on pregnant and pediatric populations.
Methodology: A systematic review of the PubMed database was conducted, identifying 220 records. Thirty-two publications meeting the criteria regarding the mechanism of action, efficacy, adverse event profile, and comparison with other disease-modifying therapies (DMTs) were included in the final analysis.
Results: The analysis demonstrated that the extended interval dosing (EID, every 6 weeks) regimen maintains clinical and radiological efficacy comparable to the standard interval dosing (SID, every 4 weeks), while significantly reducing the risk of progressive multifocal leukoencephalopathy (PML) by 88–94%. It was recognized that natalizumab is safer than other DMTs, such as ocrelizumab, without compromising efficacy. In the pediatric population, NTZ showed the highest efficacy in reducing relapse rates compared to fingolimod and injectable therapies. In pregnant women, continuing treatment until the 34th week prevents postpartum rebound relapses and improves EDSS scores, showing no teratogenic effects. Economically, the subcutaneous form of NTZ and the use of EID generate significant direct and societal cost savings.
Conclusions: Natalizumab remains a highly effective and cost-efficient therapeutic option for the treatment of relapsing-remitting MS. Personalization of treatment through the EID regimen and the subcutaneous formulation allows for an improved safety profile and patient quality of life, while simultaneously reducing the systemic burden on healthcare.

KEYWORDS

Natalizumab, Multiple Sclerosis, Demyelination, Central Nervous System Pathology, Disease Mechanisms, Neurological Symptoms, Therapeutic Approaches, Pregnancy, Side Effects

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1. Introduction

1.1Multiple Sclerosis (SM)

Multiple sclerosis (MS) is a chronic demyelinating inflammatory disease of the central nervous system. It has an immunological basis and causes neuroaxonal damage. MS affects more than 2.8 million people worldwide [2]. It typically manifests between the ages of 20 and 40 and leads to a gradual increase in disability [5]. Multiple sclerosis usually begins as a relapsing-remitting form (RRMS), which is characterized by episodic neurological symptoms followed by complete or partial recovery from disease symptoms. In approximately 10% of cases, MS manifests as a primary progressive form (PPMS) with steady progression of disability and accumulation of neurological symptoms from the onset of the disease (Lublin et al. 2014) [3].Autoreactive lymphocytes play a significant role in the cause-and-effect chain of this disease. Inflammation leads to gradual neurodegeneration [3] at an early stage. Infection with the Epstein-Barr virus (EBV) or contact with myelin antigens contributes to the development of MS through the primary activation of T lymphocytes. These migrate to the CNS, where they undergo further activation and differentiation into subpopulations: pro-inflammatory Th1 lymphocytes (secreting IFN-γ, TNF-α, IL-2, IL-12, IL-15), anti-inflammatory Th2 lymphocytes (IL-4, IL-5, IL-13), and Th17 lymphocytes (secreting IL-17, IL-21, IL-22) [7]. Increased expression of IL-17 in the cerebrospinal fluid (CSF) and blood of MS patients, particularly during relapses, suggests a key role for this cytokine in disease progression [10].Chronic inflammation induces the activation of oxidative stress enzymes. This leads to damage of proteins, lipids, carbohydrates, and nucleic acids, mitochondrial degeneration, ion channel dysfunction, and the activation of apoptotic pathways, which initiates neurodegeneration. Chronic overactivity of oxidative enzymes can sustain ongoing inflammation, contributing to the progression of MS

[10]. Progression independent of relapse activity (PIRA) and relapse-associated worsening (RAW) events are key factors determining the increase in disability. They play a role in both the short and long term [6]. It has been shown that the occurrence of a PIRA event at an early stage of the disease is a predictor of unfavorable long-term disability outcomes [6].Multiple sclerosis affects women three times more often than men, and the average age of diagnosis usually coincides with reproductive age. Consequently, an increasing number of women with MS make reproductive decisions during treatment and the use of disease-modifying therapies (DMTs). Pregnancy has a modulating effect on MS activity, especially in the third trimester, with a significant reduction in relapse frequency [6]. Rebound disease activity is particularly concerning in women who discontinue high-efficacy therapies before or during pregnancy, as therapeutic options during pregnancy may be limited due to fetal safety considerations [16].

1.2Natalizumab (NTZ)

Natalizumab (NTZ) is a humanized monoclonal IgG4 antibody that blocks the $\alpha 4$ subunit of leukocyte integrins α4β1 i α4β7. Its mechanism of action involves inhibiting the interaction of leukocytes with vascular cell adhesion molecule-1 (VCAM-1) and mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) on endothelial cells [20]. This blocks the migration of lymphocytes across the blood-brain barrier into the central nervous system [12, 20], which is crucial in the pathogenesis of relapsing-remitting multiple sclerosis (RRMS) [8, 21, 22]. Natalizumab is one of the high-efficacy therapies (HET) alongside other disease-modifying therapies (DMTs) such as ocrelizumab, ofatumumab, fingolimod, and cladribine [1]. It is used as a first-line therapy in cases of aggressive disease onset, as escalation therapy after an insufficient response to other DMTs [16, 23], or in rapidly evolving severe RRMS. The latter is defined as at least two disabling relapses within a year and at least one gadolinium-enhancing lesion on brain MRI or a significant increase in T2 lesion load compared to a previous MRI scans [12]. It was the first DMT approved by the European Medicines Agency [2] in a regimen of 300 mg every 4 weeks (standard interval dosing, SID) [24]. Currently, an extended interval dosing (EID) regimen is also used, in which natalizumab is administered at a dose of 300 mg but every 6 weeks [5]. The purpose of increasing the dosing interval is to reduce the risk of progressive multifocal leukoencephalopathy (PML) without reducing the drug's efficacy [8]. EID aims to lower the risk of PML while maintaining therapeutic effectiveness [26, 27]. This is based on the hypothesis that a partial reduction in receptor exposure to the drug may allow for some degree of restoration of the antiviral immune response, potentially decreasing the risk of PML [8, 28]. Reported adverse effects also include severe anemia [4]. There is also a SID/EID regimen involving starting therapy with SID and later switching to EID [15].In the context of natalizumab treatment, an important element to mention is the use of this drug during pregnancy. There are two primary management options: administering the drug before conception or continuing dosing in an extended interval dosing (EID) regimen of 6–8 weeks up to approximately the 34th week of pregnancy [16, 25]. The timing in this context is not accidental. This period of several weeks covers the time of maximal transplacental antibody transfer [16, 25], and natalizumab crosses the placenta mainly during the third trimester of pregnancy [16]. Hence, one regimen involves using it until the 34th week of pregnancy. Regarding the adverse effects of natalizumab on the fetus, mild and transient reversible hematological abnormalities are mentioned. These usually resolve within the first few weeks of life without leaving permanent effects [16].

1.3Pediatric-onset Multiple Sclerosis (POMS)

Multiple sclerosis usually has its onset between the ages of 20 and 50; however, approximately 3%–5% of cases begin in childhood. Patients with pediatric-onset multiple sclerosis (POMS) typically experience higher levels of inflammation with more frequent relapses than patients with adult-onset multiple sclerosis (AOMS) [18]. Treatment for this form of MS most commonly includes interferon-β and glatiramer acetate [18]. Observational studies of pediatric patients have demonstrated the efficacy of treatments including natalizumab [18].

1.4Progressive multifocal leukoencephalopathy (PML)

Diagnostic criteria for PML include progressive subacute neurological symptoms, characteristic PML imaging results, and the detection of JC virus DNA in the cerebrospinal fluid, as well as the exclusion of other diseases [13]. According to several studies, patients with antibodies against the JC virus or a history of receiving immunosuppressive therapy, after more than 2 years of natalizumab therapy, are particularly at risk of an increased risk of developing PML [8, 29, 30].

2. Methodology

A systematic search of the PubMed database was performed to locate publications addressing use of Natalizumab in multiple sclerosis, adverse effects of said drug,

Our team initially identified 220 records. Titles and abstracts were subsequently screened for relevance according to predefined eligibility criteria:

(1) human study, (2) drug mode of action and efficacy, and (3) compatibility with other DMTs, (4) study sample size, and (5) year of inception.

After full-text evaluation, 32 publications that met all inclusion criteria were selected for final analysis. No restrictions were imposed on participant gender, age, or skill level. Eligible studies were then integrated to assess natalizumab's efficacy by dosing regimen, compared to other DMTs, adverse events, and its impact on pregnant and pediatric populations.

3. Results

3.1Administration regimens

Analyzing the works on our chosen topic, we considered the efficacy of various natalizumab therapy regimens and whether the regimen with extended intervals between doses is as beneficial as SID. In a study conducted by Meral Seferoğlu et al. 2025 involving 80 patients with RRMS, participants were divided into a group of 52 individuals receiving NTZ in the SID regimen and a group of 28 individuals receiving NTZ in the EID regimen. Patients in the EID group (35 months) had a longer median duration of NTZ treatment than those in the SID group (12 months); this difference was statistically significant and consistent with the assumptions of these two regimens. The most important finding of this study was the observation of no significant differences in clinical and radiological worsening between the two dosing regimens [8]. It was also established that EID maintains efficacy while potentially reducing the risk of PML [8].

Ichiro Nakashima et al. 2026 analyzed the annualized relapse rate (ARR) before and after starting natalizumab treatment. In a study covering a population of 120 patients, the ARR decreased both in the group treated exclusively with EID (97.9% reduction in ARR from 0.95 to 0.02, $p = 0.0005$) and in the SID/EID group (91.7% reduction in ARR from 1.08 to 0.09, $p < 0.0001$). The observed decreases were statistically significant [15]. Patients in the EID-only and SID/EID groups had a longer time to the first relapse than patients in the SID-only group. The percentage of patients with new or enlarging T2 lesions on MRI was also considered depending on the type of regimen they were treated with. In all groups, the percentages of such patients decreased, most notably in the SID-only (89.1%) and SID/EID (95.7%) groups. The above information reinforces the view that EID is a viable and effective alternative to SID for many patients and significantly lowers the costs of drug acquisition and monitoring without compromising clinical benefits.

3.2Cerebrospinal fluid proteome profiling

Sahla El Mahdaoui et al. 2025 undertook the profiling of the cerebrospinal fluid proteome in progressive forms of multiple sclerosis and its changes depending on natalizumab treatment. After a 60-week period of NTZ treatment, a decrease in the concentration of 11 proteins relevant to the pathogenesis and progression of MS was observed. These included proteins associated with B lymphocytes (BCMA, SLAMF7, and IgG), T lymphocytes (granzyme A), myeloid cells (macrophage-derived chemokine (MDC) and chitinase 1 (CHIT1)), leukocyte activation (CD48 and MMP-9), and those related to cell adhesion (desmoglein-2, VCAM-1, and soluble E-selectin). All treatment effects were statistically significant [3].

3.3Adverse effects

Analysis of the safety profile of natalizumab (NTZ) compared to other disease-modifying therapies (DMTs) indicates a specific set of risks, among which infections and rare but serious neurological and hematological events predominate. Tobias Monschein et al. 2025 presented a general characterization of adverse events (AEs), which were reported in approximately 16.9% of patients treated with natalizumab. The most common included [2]: infections (6.1%)—mainly influenza, COVID-19, herpes virus infections, as well as urinary tract, upper respiratory tract, and ear infections, and pneumonia; nervous system disorders (3.8%)—primarily headaches and dizziness; and general reactions (3.4%)—fatigue (1.7%), injection site reactions (1%), flu-like symptoms (0.2%), concentration disorders (0.2%), and edema (0.2%).

Serious adverse events (SAEs) were also distinguished. Although serious events affect only about 1.3% of patients, they are of significant clinical importance. The most serious, associated with NTZ treatment, is PML (Progressive Multifocal Leukoencephalopathy), which was recorded in 0.3% of patients in registration trials. Importantly, this risk can be modified through the dosing regimen—extending the intervals between doses (EID, e.g., every 6 weeks) allows for a reduction in PML risk by 88–94% [13, 15] compared to standard

dosing every 4 weeks (SID), while maintaining similar therapeutic efficacy, as previously mentioned in our work.

SAEs also include neoplasms, which occur rarely (0.5%), and among them, breast cancer, cervical cancer, WHO grade I-II glioma, pituitary adenoma, and gastrointestinal tumors have been diagnosed. It is worth noting that higher rates of neoplasia (approx. 1.4–1.5%) are observed in the case of S1P receptor modulators (e.g., fingolimod, siponimod) [2]. Attention was also drawn to hematological disorders, where natalizumab can lead to severe anemia. This mechanism is associated with the blocking of $\alpha4\beta1$ integrin on erythroblasts, which disrupts their communication with macrophages and inhibits the maturation of red blood cells. Although anemia occurs in 1–10% of patients, its severe form is rare (0.1%) [4]. Serious infections (0.5%) were also listed—osteomyelitis (0.1%), severe pneumonia requiring hospitalization (0.1%), and urosepsis (0.1%) [2].

Compared with ocrelizumab (OCR), natalizumab presents a more favorable general safety profile—the risk of any adverse events is as much as 4.5 times higher in the OCR group [12]. Ocrelizumab more frequently causes infusion-related reactions (IRRs) and specific changes in blood parameters, such as hypogammaglobulinemia. Conversely, S1P modulators (fingolimod, siponimod) are more frequently associated with the risk of skin cancers [2] and pregnancy-related adverse events [2], which are not as clearly emphasized in population data for NTZ.

3.4Natalizumab vs Ocrelizumab

Ocrelizumab is a humanized anti-CD20 monoclonal antibody. Analysis of research results comparing natalizumab (NTZ) with ocrelizumab (OCR) indicates a very similar efficacy for both drugs across key parameters of control in relapsing-remitting multiple sclerosis (RRMS). In real-world evidence studies, no significant differences were found in the annualized relapse rate (ARR), which was 0.071 for both groups [9]. Both therapies demonstrate high efficacy in eliminating RAW (relapse-associated worsening) events and inflammatory activity in MRI studies, where the time to the appearance of new lesions did not differ between the groups. Similarly, the risk of disability progression, measured by the time to the first PIRA (progression independent of relapse activity) event and the attainment of EDSS 4.0 (1.23, 0.57–2.66; p = 0.60) and 6.0 (0.93, 0.32–2.68; p = 0.89) scores, remained comparable [6]. Although after 5 years of observation the percentage of patients maintaining NEDA-3 status (no evidence of disease activity) was slightly higher in the ocrelizumab group (65% vs. 50.5% for NTZ), this difference did not reach statistical significance [12]. Significant differences were noted, however, in the safety profile: patients using ocrelizumab showed a 4.5 times higher risk of adverse events, such as infusion reactions or infections, while simultaneously showing higher treatment durability with this molecule [12]. The stable number of patients treated with natalizumab suggests, however, a lower number of cases of treatment discontinuation compared to other highly effective drugs [1].

3.5Use of Natalizumab during pregnancy

As shown by the study of E. Le Page et al. 2025, the approach to using natalizumab (NTZ) in pregnant women has undergone significant evolution in recent years—from cautious treatment discontinuation before conception to a strategy of continuing treatment to protect maternal health. Data from the years 2019–2023 indicate a clear trend toward maintaining therapy: the percentage of women discontinuing treatment before becoming pregnant dropped from 20% to just 7–8% [1]. Currently, clinical practice increasingly allows for the continuation of drug administration during pregnancy, which is reflected in the statistics. In the first trimester (T1), treatment maintenance increased from 75% to 90%; in the second trimester (T2), an increase from 44% to nearly 78% was observed; and in the third trimester (T3), exposure affects 25–36% of pregnancies, with an upward trend, usually in cases of a severe disease course [1]. In order to minimize fetal exposure while maintaining control over the mother's disease, an extended interval dosing (EID) regimen is commonly used, most often every 6 or 8 weeks. Therapy is typically discontinued around the 34th week of pregnancy and resumed quickly after delivery (approximately 85% of women return to treatment in the first trimester of the postpartum period) [25]. Continuing NTZ treatment into late pregnancy is associated with significant clinical benefits for the mother in the postpartum period. Women continuing therapy have a significantly lower relapse rate and a lower incidence of new lesions on MRI scans (only 9.4% of patients with active gadolinium-enhancing (GdE+) lesions vs. 46,7% in the group that discontinued treatment). Additionally, in the group continuing treatment, even an improvement in EDSS scores was noted after delivery, whereas in patients discontinuing therapy, this index remained unchanged or worsened [16].

Regarding neonatal safety, studies confirm that natalizumab does not have teratogenic effects (it does not cause birth defects), even though in preclinical studies it was classified as category C in the FDA pregnancy drug classification. The birth weight, height, and head circumference of newborns exposed to the drug in utero

are comparable to WHO standards and do not deviate from the results of children born to healthy mothers [16, 31]. Due to transplacental transfer, there is a hematological risk for newborns exposed to the drug in the third trimester (after the 30th week). Mild anemia or thrombocytopenia may occur. However, these are transient effects resulting from the mechanism of blocking VLA-4 receptors on fetal blood cells [32]. In summary, the data suggest that continuing the use of natalizumab until the 34th week of pregnancy is a safe and effective strategy for women with a highly active form of MS, protecting against a sharp rebound of the disease after delivery without a negative impact on the child's overall development [16].

3.6Pediatric population with MS

Tim Spelman et al. 2024, in a study evaluating the efficacy of natalizumab for the treatment of multiple sclerosis in the pediatric population, demonstrated that this therapy was associated with a significant reduction in disease activity compared to other disease-modifying therapies (DMTs) [18]. The primary endpoint of the study was the time to the first relapse from the start of therapy, while secondary outcomes included, among others, the annualized relapse rate (ARR), the proportion of relapse-free patients in subsequent years of observation, time to treatment discontinuation, and changes in disability level on the EDSS scale. The proportion of relapse-free patients after the 1st, 2nd, and 5th years was highest in the natalizumab-treated group (94.8%, 93.4%, and 90.0%, respectively), lower in the fingolimod group (88.2%, 82.9%, 71.9%), and lowest among patients receiving injectable DMTs (73.3%, 59.8%, 35.8%) [18]. The risk of relapse with natalizumab use was significantly lower than with injectable therapy (HR 0.15; 95% CI 0.07–0.31; $p < 0.001$) and fingolimod (HR 0.37; 95% CI 0.14–1.00; $p = 0.049$). ARR values in the natalizumab group (0.08 [0.05–0.11]) and the fingolimod group (0.12 [0.08–0.16]) were significantly lower than among patients receiving injectable DMTs (0.35 [0.33–0.38]; $p < 0.0001$), although the differences between natalizumab and fingolimod did not reach statistical significance. These results indicate that natalizumab provides high clinical efficacy in reducing relapse frequency and the risk of disease progression in children and adolescents with multiple sclerosis [18].

4. Discussion

Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system that places an enormous burden on patients, society, and payers. The management of relapsing-remitting multiple sclerosis (RRMS) has been transformed by the introduction of high-efficacy disease-modifying therapies (DMTs). Among them, natalizumab (NTZ) remains a key element of treatment, distinguished not only by its clinical efficacy but also by its unique mechanism of action, which—unlike anti-CD20 monoclonal antibodies or alemtuzumab—does not rely on lymphocyte depletion [8]. An analysis conducted by Luca Prosperini et al. 2025, using a cost-consequence analysis (CCA) model, provides a comprehensive overview of the clinical, economic, and social impacts of NTZ use compared to other high-efficacy therapies, namely ocrelizumab (OCR) and ofatumumab (OFA) [5]. According to long-term clinical data, natalizumab demonstrates a strong ability to inhibit disease activity. In the studied model, 5-year NTZ therapy resulted in a numerical reduction in the number of relapses compared to ocrelizumab (-5.52 per 100 patients) [5] and showed a favorable trend in slowing disability progression. Although these differences did not reach statistical significance, they correlate with an increase in quality-adjusted life years (QALYs) gained by patients, highlighting the drug's value in preserving long-term functional ability. The application of the CCA model allowed for a multi-perspective assessment, which is particularly valuable for healthcare payers focused on patient-oriented outcomes. The most striking conclusion from this study is the significant reduction in total direct costs associated with natalizumab. Over a 5-year period, NTZ therapy generated savings of approximately 1,604,423 EUR and 1,368,817 EUR per 100 patients compared to ocrelizumab and ofatumumab, respectively [5]. These savings result primarily from switching from a 4-week to a 6-week regimen after the first year of treatment, which significantly lowered drug acquisition and monitoring costs without compromising clinical benefits. The introduction of the subcutaneous route of administration optimized resource utilization, which also contributed to cost reduction. Data presented in the study show that NTZ in the SC form significantly reduced treatment chair time (by 2,933 hours per 100 patients) and decreased the workload of doctors and nurses [5]. Beyond direct medical costs, natalizumab showed a positive trend in reducing the societal burden of MS. Treatment was associated with a reduction in productivity loss (316 fewer days than OCR and 1,091 fewer days than OFA per 100 patients) [5]. For patients, switching to subcutaneous administration saved 5,589 hours over five years, while caregivers experienced a significant reduction in lost productivity. These results highlight the benefits of using natalizumab. Despite high efficacy, the risk of progressive multifocal leukoencephalopathy (PML) remains a critical aspect of NTZ therapy, with a global incidence rate of approximately 3.43 cases per 1,000 treated patients [13]. Risk stratification remains essential, especially regarding prior use of immunosuppressive drugs.

However, the implementation of the EID regimen is expected to further mitigate this risk, representing a key evolution in the safety profile of NTZ. Interestingly, rare cases of PML are still being monitored worldwide, including in EID regimens, which requires constant vigilance and rigorous surveillance protocols [13]. Although the choice of DMT must remain individualized, the data presented in this CCA analysis provide decision-makers with compelling evidence of the enduring relevance and economic advantage of natalizumab in a competitive therapeutic field.

5. Conclusions

Analyzing the selected articles, we have reached several significant conclusions. Natalizumab significantly reduces the concentration of proteins key to the pathogenesis and progression of MS, including biomarkers of B-cell, T-cell, and myeloid cell activation. It demonstrates high efficacy in inhibiting inflammatory activity as measured by the ARR index and MRI imaging activity. Regarding the dosing regimen, extending the intervals between doses (EID) to 6 weeks serves as a safe and effective alternative to the standard regimen; furthermore, it allows for a significant reduction in the risk of PML (by approximately 90%) while maintaining disease control, making it preferred for long-term patients or those in high-risk groups. Considering the safety and tolerability of natalizumab, we concluded that serious adverse events (SAEs) affect a small percentage of patients (1.3%), yet they require close supervision. Nevertheless, natalizumab is characterized by a more favorable overall safety profile than ocrelizumab, exhibiting a 4.5-fold lower risk of adverse events, which translates into greater treatment stability and durability. We paid particular attention to two unique populations—pregnant women and the pediatric population. Continuing treatment until the 34th week of pregnancy is an effective strategy for preventing disease activity in the mother. Despite the risk of transient hematological disorders in the newborn, there is no evidence of teratogenic effects or disturbances in anthropometric parameters. Among children with MS, NTZ treatment ensures the highest percentage of relapse-free patients compared to fingolimod and first-line drugs. It constitutes a key therapy for aggressive forms of MS in children. Additionally, it is worth noting the economic benefits of introducing the subcutaneous (SC) formulation and the EID regimen. Both changes significantly unburden the healthcare system by reducing monitoring costs, staff workload, and the time patients spend at the facility. Furthermore, this therapy effectively reduces societal costs by limiting productivity loss for both patients and their caregivers.

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REFERENCES

1. Le Page, E., Emery, C., Fravalo, A., Fagnani, F., & Clement, A. (2025). Trends in the real-world management of patients with active relapsing-remitting multiple sclerosis treated with natalizumab (TYSABRIW) in France: An analysis of the PMSI database over five years (2019–2023). *Revue Neurologique, 181*, 535–543. https://doi.org/10.1016/j.neurol.2025.03.001
2. Monschein, T., Untersteiner, H., Ponleitner, M., Krajnc, N., Zrzavy, T., Bsteh, G., Rommer, P., Kornek, B., Enzinger, C., Di Pauli, F., Kraus, J., Guger, M., Leutmezer, F., Berger, T., & The Austrian MS Treatment Registry (AMSTR). (2025). Safety of disease modifying therapies in multiple sclerosis: Real world data from the Austrian MS Treatment Registry (AMSTR). *Journal of Neurology, 272*, 774. https://doi.org/10.1007/s00415-025-13473-7
3. El Mahdaoui, S., Kosa, P., Komori, M., Veiga González, J. L., Højsgaard Chow, H., Ratzer, R., Gøbel Madsen, C., Siebner, H. R., Bielekova, B., Villar, L. M., Christensen, J. R., & Sellebjerg, F. (2025). Profiling the cerebrospinal fluid proteome in progressive multiple sclerosis: Treatment effects and associations with IgM oligoclonal bands. *Journal of Neuroimmune Pharmacology, 20*, 98. https://doi.org/10.1007/s11481-025-10263-w
4. Hamnvik, L. H. D., Tjønnfjord, G. E., Spetalen, S., & Dalgaard, J. (2024). Long-lasting severe anemia following treatment with natalizumab for relapsing–remitting multiple sclerosis: A case report. *Journal of Medical Case Reports, 18*, 245. https://doi.org/10.1186/s13256-024-04562-8
5. Prosperini, L., Brescia Morra, V., Fornari, C., Santoni, L., Perini, D., Bergamaschi, R., & Cortesi, P. A. (2025). Cost consequence analysis of natalizumab compared with other high efficacy treatments in patients with relapsing–remitting multiple sclerosis. *PharmacoEconomics, 43*, 1463–1477. https://doi.org/10.1007/s40273-025-01539-3
6. Iaffaldano, P., Lucisano, G., Guerra, T., Paolicelli, D., Portaccio, E., Inglese, M., Foschi, M., Patti, F., Granella, F., Romano, S., Cavalla, P., De Luca, G., Gallo, P., Bellantonio, P., Gallo, A., Montepietra, S., Di Sapio, A., Vianello, M., Quatrale, R., . . . Trojano, M. (2024). A comparison of natalizumab and ocrelizumab on disease progression in multiple sclerosis. *Annals of Clinical and Translational Neurology, 11*(8), 2008–2015. https://doi.org/10.1002/acn3.52118
7. Finocchiaro, C., Chisari, C. G., Lo Fermo, S., D'Amico, E., Parrinello, N. L., Romano, A., Palumbo, G. A., Marino, S., Corsale, A. M., Di Raimondo, F., Zappia, M., & Patti, F. (2025). In vivo effects of disease-modifying therapies on immunological subsets in patients with relapsing-remitting multiple sclerosis. *Current Neuropharmacology, 23*(13), 1783–1796. https://doi.org/10.2174/011570159X360729250319064959
8. Seferoğlu, M., Tunç, A., Sıvacı, A. Ö., Piri Çınar, B., Destan Bünül, S., Ethemoğlu, Ö., Yalaz Tekan, Ü., & Yetkin, M. F. (2025). Comparative efficacy and safety of extended versus standard interval dosing of natalizumab in relapsing–remitting multiple sclerosis patients: A multicenter analysis. *CNS Neuroscience & Therapeutics, 31*, e70445. https://doi.org/10.1111/cns.70445
9. Maersk-Moller, C., Pontieri, L., Stilund, M. L. M., Christensen, J. R., Storr, L. K., Hansen, V., Schäfer, J., Weglewski, A., Quinto Romani, K., Jensen, H. B., Kant, M., Illes, Z., Papp, V., Sejbaek, T., Torring, C. W., Sellebjerg, F., Poulsen, M. B., & Magyari, M. (2025). A national Danish effectiveness study of ocrelizumab versus natalizumab in multiple sclerosis. *European Journal of Neurology, 33*, e70507. https://doi.org/10.1111/ene.70507
10. Adamczyk, B., Morawiec, N., Zalejska-Fiolka, J., Kwinta, R., Rakoca, M., Wawrzyniak, S., Sowa, A., Sawa, K., & Adamczyk-Sowa, M. (2025). Evaluation of selected serum adipocytokines in patients with relapsing–remitting multiple sclerosis treated with immunomodulatory second-line drugs. *International Journal of Molecular Sciences, 26*, 8070. https://doi.org/10.3390/ijms26168070
11. Chisari, C. G., Aguglia, U., Amato, M. P., Bergamaschi, R., Bertolotto, A., Bonavita, S., Brescia Morra, V., Cavalla, P., Cocco, E., Contel, A., Cottone, S., De Luca, G., Di Sapio, A., Filippi, M., Gallo, A., Gasperini, C., Granella, F., Lus, G., Maimone, D., . . . Patti, F. (2024). Long-term effectiveness of natalizumab in secondary progressive multiple sclerosis: A propensity-matched study. *Neurotherapeutics, 21*, e00363. https://doi.org/10.1016/j.neurot.2024.e00363
12. Barbuti, E., Castiello, A., Pozzilli, V., Carotenuto, A., Tomasso, I., Moccia, M., Ruggieri, S., Borriello, G., Lanzillo, R., Brescia Morra, V., Pozzilli, C., & Petracca, M. (2025). Comparative effectiveness, safety and persistence of ocrelizumab versus natalizumab in multiple sclerosis: A real-world, multi-center, propensity score-matched study. *Neurotherapeutics, 22*, e00537. https://doi.org/10.1016/j.neurot.2025.e00537
13. Takahashi, K., Nakahara, J., Miura, Y., Ae, R., Nakamichi, K., Harada, M., Mori, K., Sanjo, N., Yukitake, M., Yokote, H., Hamaguchi, T., Yamada, M., & Takao, M. (2025). Natalizumab-associated progressive multifocal leukoencephalopathy after natalizumab extended interval dosing therapy in Japan. *Neurology: Neuroimmunology & Neuroinflammation, 12*, e200476. https://doi.org/10.1212/NXI.0000000000200476
14. Gelissen, L. M. Y., van Oosten, B. W., Hogenboom, L., de Jong, B. A., Toorop, A. A., Killestein, J., Strijbis, E. M. M., & van Kempen, Z. L. E. (2025). Wearing-off symptoms persist in the majority of patients with multiple sclerosis after switching from natalizumab to ocrelizumab. *Journal of the Neurological Sciences, 479*, 125652. https://doi.org/10.1016/j.jns.2025.125652
15. Nakashima, I., Ohashi, T., Yokoyama, K., Kaida, K., Nakahara, J., Kondo, T., Yoshikura, N., Shimizu, Y., Nohara, C., Sakurai, K., Yokote, H., Niino, M., Yamamura, T., Fujihara, K., Isobe, N., Ochi, H., Mori, M., Kawachi, I., Shimizu, F., . . . Fukazawa, T. (2026). A multicenter, retrospective study in patients with multiple sclerosis treated with natalizumab in a real-world setting in Japan: The REFIND study. *Multiple Sclerosis and Related Disorders, 107*, 107007. https://doi.org/10.1016/j.msard.2026.107007

16. Kitsos, D. K., Stavrogianni, K., Dimitriadou, E.-M., Giannopapas, V., Akrivaki, A., Chasiotis, A. K., Roussos, F., Tagaris, G., Tsivgoulis, G., Mastorodemos, V. C., & Giannopoulos, S. (2026). Maternal and neonatal outcomes following natalizumab use during pregnancy in women with multiple sclerosis: A multicenter observational study. *Journal of Clinical Neuroscience, 148*, 111977. https://doi.org/10.1016/j.jocn.2026.111977
17. Hellgren, J., Ahlstrom, I., Fornvik Jonsson, M., Compagno Strandberg, M., Hansson, O., Janelidze, S., Svenningsson, A., & Kallen, K. (2025). Comparison of CSF biomarkers in multiple sclerosis patients treated with natalizumab and rituximab. *Multiple Sclerosis and Related Disorders, 99*, 106479. https://doi.org/10.1016/j.msard.2025.106479
18. Spelman, T., Simoneau, G., Hyde, R., Kuhelj, R., Alroughani, R., Ozakbas, S., Karabudak, R., Yamout, B. I., Khoury, S. J., Terzi, M., Boz, C., Horakova, D., Kubala Havrdova, E., Weinstock-Guttman, B., Patti, F., Altintas, A., Mrabet, S., Gouider, R., Inshasi, J., . . . Butzkueven, H. (2024). Comparative effectiveness of natalizumab, fingolimod, and injectable therapies in pediatric-onset multiple sclerosis. *Neurology, 102*, e208114. https://doi.org/10.1212/WNL.0000000000208114
19. Al-Araji, S., Moccia, M., Jha, A., Zhang, L., Eshaghi, A., Kanber, B., Bianchi, A., Yam, C., Abdel-Mannan, O., Goodkin, O., Pontillo, G., Hamed, W., Mohamud, S., Brownlee, W. J., Chard, D. T., Chataway, J., Chung, K., De Angelis, F., Hammam, A., . . . Ciccarelli, O. (2025). Effectiveness of disease-modifying therapies in patients with late-onset relapsing-remitting multiple sclerosis. *Neurology, 105*, e213967. https://doi.org/10.1212/WNL.0000000000213967
20. Khoy, K., Mariotte, D., Defer, G., Petit, G., Toutirais, O., & Le Mauff, B. (2020). Natalizumab in multiple sclerosis treatment: From biological effects to immune monitoring. *Frontiers in Immunology, 11*, 549842. https://doi.org/10.3389/fimmu.2020.549842
21. Polman, C. H., O'Connor, P. W., Havrdova, E., et al. (2006). A randomized placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *New England Journal of Medicine, 354*, 899–910. https://doi.org/10.1056/NEJMoa044397
22. Stuve, O., & Bennett, J. L. (2007). Pharmacological properties, toxicology, and scientific rationale for the use of natalizumab (Tysabri) in inflammatory diseases. *CNS Drug Reviews, 13*(1), 79–95. https://doi.org/10.1111/j.1527-3458.2007.00003.x
23. Freedman, M. S., Clift, F., Devonshire, V., et al. (2025). First-line use of higher-efficacy disease-modifying therapies in multiple sclerosis: Canadian consensus recommendations. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*, 1–10. https://doi.org/10.1017/cjn.2025.10342
24. Ryerson, L. Z., Foley, J., Chang, I., Kister, I., Cutter, G., Metzger, R. R., et al. (2019). Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. *Neurology, 93*(15), e1452–e1462. https://doi.org/10.1212/WNL.0000000000008243
25. Dobson, R., Dassan, P., Roberts, M., Giovannoni, G., Nelson-Piercy, C., & Brex, P. A. (2019). UK consensus on pregnancy in multiple sclerosis: Association of British Neurologists guidelines. *Practical Neurology, 19*(2), 106–114. https://doi.org/10.1136/practneurol-2018-002060
26. Zhovtis Ryerson, L., Frohman, T. C., Foley, J., et al. (2016). Extended interval dosing of natalizumab in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry, 87*, 885–889. https://doi.org/10.1136/jnnp-2015-312940
27. Bomprezzi, R., & Pawate, S. (2014). Extended interval dosing of natalizumab: A two-center 7-year experience. *Therapeutic Advances in Neurological Disorders, 7*, 227–231. https://doi.org/10.1177/1756285614540224
28. Clerico, M., De Mercanti, S. F., Signori, A., et al. (2020). Extending the interval of natalizumab dosing: Is efficacy preserved? *Neurotherapeutics, 17*(1), 200–207. https://doi.org/10.1007/s13311-019-00776-7
29. Bloomgren, G., Richman, S., Hotermans, C., et al. (2012). Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *New England Journal of Medicine, 366*(20), 1870–1880. https://doi.org/10.1056/NEJMoa1107829
30. Ho, P. R., Koendgen, H., Campbell, N., Haddock, B., Richman, S., & Chang, I. (2017). Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: A retrospective analysis of data from four clinical studies. *The Lancet Neurology, 16*, 925–933. https://doi.org/10.1016/S1474-4422(17)30282-X
31. Hellwig, K., Haghikia, A., & Gold, R. (2011). Pregnancy and natalizumab: Results of an observational study in 35 accidental pregnancies during natalizumab treatment. *Multiple Sclerosis Journal, 17*(8), 958–963. https://doi.org/10.1177/1352458511401944
32. Wehner, N. G., Shopp, G., Oneda, S., & Clarke, J. (2009). Embryo/fetal development in cynomolgus monkeys exposed to natalizumab, an α4 integrin inhibitor. *Birth Defects Research Part B: Developmental and Reproductive Toxicology, 86*(2), 117–130. https://doi.org/10.1002/bdrb.20190