Natalizumab extended-interval dosing in multiple sclerosis to mitigate progressive multifocal leukoencephalopathy risk: initial study evidence and real-world experience

Journal of Central Nervous System Disease
Volume 14: 1–6

DOI: 10.1177/11795735221135485
SAGE

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ABSTRACT

The high efficacy of natalizumab in the treatment of relapsing-remitting multiple sclerosis (MS) is without controversy. Indeed, effective disease control was not only demonstrated in the pivotal trials but has been corroborated impressively in real-world observations. This monoclonal IgG4 antibody blocks the α4β1 integrin-mediated leukocyte-endothelial interaction and thereby inhibits the migration of immune cells to the brain parenchyma. However, treatment with natalizumab carries the risk of progressive multifocal leukoencephalopathy (PML). This potentially lethal side effect is a significant limitation for treatment initiation and long-term therapy. Natalizumab is given intravenously or subcutaneously in the standard dose of 300 mg every 4 weeks, allowing drug concentrations at levels that ensure continuous α4β1 integrin receptor saturation on the surface of immune cells. Extended-interval dosing (EID) is an emerging treatment approach that aims to mitigate the natalizumab-related PML risk by prolonging the standard infusion intervals to 6 weeks or even more. This treatment approach may abrogate the PML risk due to improved immune surveillance within the central nervous system while maintaining clinical efficacy. Moreover, even an individual interval dosing can be envisioned based on the availability of a biomarker that is capable of monitoring both safety and efficacy aspects. This review summarizes the early and encouraging evidence for EID from observational and randomized-controlled trials and discusses current limitations and upcoming challenges for introducing a tailored treatment approach.

KEYWORDS: Natalizumab, multiple sclerosis, extended-interval dosing, progressive multifocal leukoencephalopathy, individualized treatment, disease-modifying drug

TYPE: Review

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JP received a honorarium for lecturing from Sanofi. JS received honoraria for lectures, the assembly of teaching material or participation in advisory boards from Alexion, Angelini, BMS, Biogen, Boehringer, Horizon, Janssen, Merck, Novartis, Immunic, Roche, Sandoz and Sanofi.

FUNDING: The authors received no financial support for the research, authorship, and/or publication of this article.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) with pathological hallmarks of demyelination and axonal loss.[1] The humanized monoclonal immunoglobulin (Ig)G4 antibody natalizumab (Tysabri®; Biogen-Idec, Cambridge, MA, USA) is a highly efficacious treatment for relapsing-remitting MS.[2] Natalizumab blocks the α4-integrin-mediated leukocyte-endothelial interaction and thereby inhibits the trafficking of immune cells from the blood to the central nervous system (CNS).[3,4] The United States (U.S.) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved natalizumab as single disease-modifying therapy in adults with highly active relapsing-remitting multiple sclerosis upon 2 convincing pivotal phase III trials.[5,6] The AFFIRM trial investigated the efficacy and safety of natalizumab as monotherapy, whereas the SENTINEL trial evaluated the efficacy and safety of natalizumab in combination with intramuscular IFN-β-1a (Avonex®). A fixed four-weekly intravenous (IV) dose of 300 mg was chosen for the phase III trials, resulting in a 3.0-6.0 mg/kg dose for patients with body weights ranging from 50 to 100 kg to ensure a stable receptor saturation.[7] In the meantime, more than a dozen post-approval studies corroborated the high efficacy on clinical disease activity and inflammatory hallmarks on magnetic resonance imaging (MRI).[8] The EMA granted market authorization for subcutaneous (SC) natalizumab in April 2021. The decision was based on the DELIVER and REFINE studies, which showed comparability of the IV and SC administration of 300 mg natalizumab in terms of efficacy, pharmacokinetic and pharmacodynamic profiles.[9,10]

However, treatment with natalizumab is associated with an increased risk of progressive multifocal leukoencephalopathy (PML). This rare infection is caused by a pathogenic form of John Cunningham Polyomavirus (JCPyV), commonly referred to as John Cunningham virus (JCV). The JCV antibody index is used for the risk assessment of natalizumab-associated PML.[11,12] In this article, we summarize real-world evidence for extended-interval dosing (EID) of natalizumab, an emerging treatment concept aimed

at mitigating the risk for this potentially fatal opportunistic brain infection.

Natalizumab treatment increases the risk of PML

The two main concerns with natalizumab treatment in people with MS (pwMS) are the risk of developing PML and disease rebound after the termination of the monthly infusions.[13,14] PML is strongly associated with, although not limited to, immunosuppressed status and predominantly occurs in individuals with acquired immunodeficiency syndrome (AIDS).[15] A pooled analysis of 4 large, observational, open-label studies provided valuable insights into PML risk associated with natalizumab treatment.[16] In JCV antibody-positive pwMS with previous immunosuppressant use, the estimated cumulative PML probability over 6 years is 2.7% (95% Confidence Interval (CI) 1.8-4.0), and 1.7% (95% CI 1.4-2.1) in those without this pre-treatment. The category "immunsupprosive drugs" comprised mitoxantrone, methotrexate, azathioprine, cyclophosphamide, mycophenolate, ciclosporin, tacrolimus, docetaxel, fluorouracil, and temsirolimus. Moreover, in pwMS without previous immunosuppressive drug therapy, the estimated annual PML risk per 1000 individuals can be stratified according to the treatment duration. The risk ranges from .01 (.00-.03) in year 1 to .6 (.0-1.5) in year 6 for people with a JCV-antibody index of ≤.9 or less; from .1 (.0-.2) in year 1 to 3.0 (.2-5.8) in year 6 for those with an index ≥.9-1.5; and from .2 (.0-.5) in year 1 to 10.0 (5.6-14.4) in year 6 for those with an index of >1.5. In addition, the duration of natalizumab treatment is another established risk factors for PML in pwMS, and is used together with the JCV antibody index for the stratification of the individual PML risk. Yet, the absolute numbers of natalizumab-associated PML cases did not diminish over time, pointing to difficulties implementing the risk-stratification algorithm in clinical practice.[17] More recently, there is evidence of different PML incidence in the U.S. versus Europe and the consideration of a higher risk for JCV antibody-negative patients than previously reported.[18] Interestingly, the risk of PML on natalizumab, in general, does not only reach a plateau but seems to decrease after about 5 years of continuous dosing.[18]

Extended-interval dosing - an emerging strategy to mitigate the PML risk

Clinicians treating pwMS at risk of PML must consider continuing treatment with natalizumab or switching to another highly-effective therapy.[19] The standard-interval dosing (SID) for natalizumab is a 300 mg infusion or SC application every 4 weeks. After a single IV administration of natalizumab, the maximal α4β1 integrin saturation is maintained for 3 to 4 weeks, and saturation declines to 50%-80% over the following 4 weeks.[20] The SID with 300 mg natalizumab was selected to provide more than 80% saturation of mononuclear cell α4β1-integrin receptors up to 1 month after administration.[21] More recent data indicate that a receptor occupancy of >50% is sufficient for effective disease control.[22] In addition, overdosing of natalizumab with subsequent restricted CNS immune surveillance and emergence of JCV mutations may be the key factor related to the occurrence of PML. Extending the interval between administrations may be a potential option to lower the risk of PML. Model-based simulations of pharmacodynamics (PD) and –kinetics (PK) revealed that every-5-week or 6-week dosing is capable to maintain the efficacy of natalizumab, at body weights <80 kg.[23,24] Indeed, several studies disclosed that body weight is a significant PD/PK variable of NTZ treatment. The partial desaturation of α-integrin receptors might enhance immune surveillance within the CNS and subsequently, reduce the risk of PML. Indeed, studies in an experimental model of viral meningoencephalitis provided a mechanistic explanation for insufficient virus control under altered T cell migration conditions.[25] The most recent EMA product information concludes that "the efficacy of natalizumab when administered with EID has not been established; therefore, the benefit/risk balance of EID is unknown".[26]

The measurement of free natalizumab and receptor saturation provides information to assess individual treatment responses.[27,28] In a cross-sectional assessment of pwMS who received SID or EID, serum natalizumab concentrations and α4-integrin receptor saturation on immune cells were analyzed in blood samples obtained at trough time points.[29] The study objective was to determine whether the steady-state pharmacologic parameters of NTZ EID, determined after at least 18 months of continuous EID treatment, would maintain α4-integrin saturation in the submaximal but "therapeutic" (>50%) range and serum concentration ≥2 μg/mL. The authors concluded that at least 9 natalizumab infusions/year are required to stay above this therapeutic threshold. Moreover, a higher body mass index was identified as a predictor of suboptimal trough saturation on EID natalizumab. Indeed, mathematical modeling using data from the RESTORE trial indicated that dosing every 5 or 6 weeks is likely to maintain the efficacy of natalizumab, particularly at body weights <80 kg, in patients who switch after a period of stability on every-four-week dosing.[23] A retrospective analysis of the TOUCH registry (Class III evidence) provided initial assurance for a significantly lower PML risk using the EID scheme after switching from SID dosing.[30]

Hereinafter, we summarize the early evidence for EID by summarizing the available scientific literature until Jul 62 022. The search revealed 6 studies concerning the efficacy, 4 studies evaluating the safety, and additional studies assessing side effects and biomarkers of EID.

Efficacy

The NOVA study was a randomized, controlled, open-label, phase 3b trial that evaluated the efficacy of IV natalizumab EID (once every 6 weeks) among participants who had previously been treated with IV natalizumab SID (once every 4 weeks) for at least 12 months (ClinicalTrials.gov Identifier: NCT03689972), in

comparison to continued IV SID treatment.[31,32] The primary endpoint was the number of new or newly enlarging T2 hyperintense lesions at week 72. A total of 499 patients were enrolled in the EID (n = 251) and SID (n = 248) groups. The study revealed a numerical difference between the 2 groups for new or newly enlarging T2 lesions at the study endpoint. In detail, the mean number of new or newly enlarging T2-lesions was .2 (95% CI .07-.63) in the EID group and .05 (.01-.22) in the SID group under the primary estimand (P = .076). The findings were driven by 2 patients with very high numbers of new or enlarging lesions (≥25) in the EID group and lower than expected disease activity in the SID group. In addition, there was 1 case of asymptomatic PML in the EID group, reinforcing the continued need for monitoring and risk stratification in all patients on natalizumab.

The multicenter study by De Mercanti et al. retrospectively analyzed data collected at 14 Italian MS centers over 11 years.[33] In total, 360 patients were studied with a mean interval of 5.3 weeks between the doses of IV natalizumab in the 6 months following the month 24 infusion. In the 2 years of follow-up, the SID and EID groups showed a comparable risk of developing active lesions on MRI.

The two-center study of Bomprezzi and Pawate reports their seven-year experience from a cohort of patients who received IV natalizumab at six-to 8-week intervals instead of SID.[34] A total of 361 patients received natalizumab for 22 ± 13 months; the minimum duration was 6 months. Of these, 96 patients received EID natalizumab at some point for 20 ± 11 months. The retrospective analysis revealed no significant difference between the relapse rate with SID vs. EID dosing (13% each). The authors note that this relapse rate is in line with other studies from the real-world setting. The number of new MRI lesions was 11% for SID and 9% for EID, respectively.

The multicenter retrospective study by Chisari et al. analyzed a total of 2092 pwMS; 40.1% received IV natalizumab according to EID.[35] At 12 and 24 months, no differences in annualized relapse rate and disability status were found. Furthermore, the progression index and confirmed disability worsening were similar between the 2 groups.

Butzkueven et al. used data as of November 2019 of the Tysabri Observational Program (TOP), an ongoing, open-label, multicenter, prospective observational study of the safety and effectiveness of IV natalizumab in patients with relapsing-remitting MS treated in real-world clinical practice settings.[36] In this study, 219 patients with natalizumab dosing every 6 weeks after 1 year of SID were matched at the time of the dosing switch. There were no significant differences in annualized relapse rates, risk of relapse, or risk of Expanded Disability Status Scale (EDSS) worsening between patients who switched to 6-week dosing and those who remained on SID.

MRI outcomes of patients treated with IV natalizumab EID versus SID in MS PATHS (Multiple Sclerosis Partners Advancing Technology and Health Solutions) were studied by Ryerson et al.[37] MS Paths is a collaborative, multicenter learning health system that generates real-world clinical and MRI data using highly standardized acquisition protocols. The MRI outcome measures included the number and volume of T2 lesions and brain atrophy. No statistical differences for MRI outcomes were observed with natalizumab EID (patients n = 79) and SID (n = 354), indicating comparable real-world effectiveness on quantitative MRI metrics.

Safety

A retrospective observational study by Riancho et al followed 39 pwMS treated with IV natalizumab over 7 years.[38] Patients were initially treated with SID over a mean time of 54 months (standard deviation (SD) 29) and later switched to EID with the administration of natalizumab every 8 weeks. The mean time on EID was 76 months (SD 13). EID maintainted its impact on relapse rate, radiological activity, and disability worsening. There were no cases of PML or other severe adverse reactions in this cohort.

Yamout et al. reported a similar observation in a cohort of 85 pwMS receiving IV natalizumab with an EID between 5 and 8 weeks for at least 6 months.[39] Natalizumab was used as escalation therapy due to persistent disease activity on baseline therapy in most patients. In a subgroup analysis of 55 patients, adverse effects were even lower in the EID group, a finding mainly related to lower rates of infections. In this regard, the 10-year interim analysis of the Tysabri Observational Programme (TOP) revealed that overall, 829 patients (13.5%) experienced ≥1 serious adverse event (SAE), with infection the most common (4.1%).[40]

A retrospective cohort study including over 35.000 JCV antibody-positive pwMS by Ryerson et al. disclosed a possible risk reduction in the EID group compared to the SID group.[30] For the primary and secondary analyses, the relative risk reduction was 94% and 88% in favor of EID; the tertiary included no cases of PML, corroborating a lower risk than SID.

Factors associated with poor functional outcome from natalizumab-associated PML include advanced age, higher initial JCV copy number in cerebrospinal fluid, and more extensive PML lesions on the initial MRI.[41] Interestingly, there was no association between functional outcome and the duration of natalizumab therapy. A case study by Scarpazza et al. raised speculations that PML In EID treated pwMS may have a more benign clinical course and outcome compared to SID.[42] The reports on 4 natalizumab-PML cases on EID showed that the patients developed PML after at least 38 natalizumab infusions. The JCV index was >1.5 in all, and no patient had received immunosuppressive therapies. Two patients were asymptomatic at PML onset, while 2 had mild motor impairment of the right hand and anomia, respectively. All patients had MRI findings compatible with immune reconstitution, and the clinical outcome was favorable (ΔEDSS up to 1).

Side effects

Individuals receiving natalizumab may report increased fatigue and other symptoms shortly before their next scheduled infusion. This phenomenon is known as the wearing-off phenomenon and is not associated with increased disease activity.[43] A recent study demonstrated low receptor occupancy in conjunction with high BMI as the underlying cause.[44] However, in a prior study, the wearing-off effect was more frequently reported in the SID (39%) than in the EID (19%).[45] The latter findings stem from a single-center study by Kempen et al, which assessed the prevalence of this phenomenon and evaluated the relationship of its occurrence to the interval between natalizumab infusions [SID vs. EID (5-7 weeks)] in 93 adults with relapsing-remitting MS and ≥ 6 consecutive infusions. The wearing-off effect was more frequent in the SID (39%) than in the EID group (19%). Moreover, no associations were found with the number of infusions, disease duration, age, or sex. Indeed, no pharmacodynamic or pharmacokinetic associations could be identified so far, which points at a potential placebo effect of the wearing-off phenomenon. In addition, a multicenter study by Dekeyser et al hypothesized that end-of-dose interval symptoms might be explained by variability in serum cytokine levels during natalizumab treatment.[46] Out of 42 patients with relapsing-remitting MS, almost 60% reported wearing-off symptoms. However, Il-6, IFN-γ and TNF-α serum levels did not correlate with the wearing-off symptoms.

Biomarkers

Low L-selectin (CD62 L) expression on the surface of $CD4^+$ T cells was proposed in 2013 as a potential biomarker indicative of the individual PML risk during natalizumab treatment.[47] Admittedly, there has been controversy about this observation, as other groups could not validate this biomarker because of methodological challenges.[48]

In 2019 an observational study by Schwab et al collected samples of 1108 pwMS and measured cell-bound CD62 L levels alongside natalizumab therapy. The authors first reported that lower CD62 L expression is associated with natalizumab treatment and a higher likelihood of developing a PML. Secondly, cessation of natalizumab or extension of treatment intervals led to recovered CD62 L values. The authors subsequently suggested that CD62 L might be evaluated as a potential biomarker in future studies for balancing efficacy and safety in EID.[49]

In a similar effort to optimize and personalize natalizumab therapy, a multicenter study by Punet-Ortiz et al. measured serum levels of natalizumab and expression of α4β1 integrin on the surface of peripheral blood lymphocytes.[50] Their results indicate a dose-dependent relationship between serum drug concentrations and α4β1 integrin surface expression. Using this method, they propose the possibility of identifying patients with suboptimal treatment and those that might benefit from an EID.

Berkovich et al. took a different approach by assessing whether CD4 cell counts correlate with different natalizumab treatment phases in pwMS, including a 12-week planned treatment interruption.[51] The authors observed that the CD4 cell count increased from baseline while on treatment and decreased back to baseline levels off treatment, then rose similarly on natalizumab reinitiation. Thus, CD4 cell counts may reflect lymphocyte trafficking and cell redistribution during natalizumab therapy and aid in individual safety monitoring during EID.

Conclusion

Despite the approval of several other disease-modifying drugs, natalizumab remains a highly effective treatment option. Some observational studies even reported a more significant impact on disease activity in clinical practice than in the active treatment arm of the AFFIRM trial.[11] The current standard is natalizumab termination in patients at high risk for PML and switch to other disease-modifying drugs.[52] In this review, we summarized the early but encouraging evidence for the short-term efficacy of natalizumab EID in combination with lower PML risk reported in observational studies. At the current stage, natalizumab EID can be seen as an emerging option for patients with lower PML risk. It needs to be taken into account that EID can also be cost-saving and may increase the quality of life due to fewer infusions and a lower frequency of hospital visits.[7] Given that the currently ongoing studies can confirm the current evidence on efficacy and safety, a reliable and easy-to-use biomarker to guide this individualized treatment concept in clinical practice will be essential. In this regard, the NEXT-MS trial (ClinicalTrials.gov Identifier: NCT04225312) aims to test feasibility and validate safety of personalized EID of natalizumab in a large real-life cohort in a Nation-wide study (the Netherlands).[53] Personalized dosing is based on natalizumab trough concentration, with an aim of natalizumab trough concentration of 10mcg/ml. The investigators plan to recruit 300 patients with a follow-up of 104 weeks, the estimated primary completion date according to clinicaltrials.gov is January 12 024.

Author contributions

JP and JS conceptualized, drafted and revised the manuscript. Both authors approved the final version.

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REFERENCES

1. Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. *N Engl J Med*. 2018; 378:169-180. doi:10.1056/NEJMra1401483.

2. Findling O, Sellner J. Second-generation immunotherapeutics in multiple sclerosis: Can we discard their precursors? *Drug Discov Today*. 2021;26:416-428. doi:10.1016/j.drudis.2020.11.022.
3. Stuve O, Marra CM, Jerome KR, et al. Immune surveillance in multiple sclerosis patients treated with natalizumab. *Ann Neurol*. 2006;59:743-747. doi:10.1002/ana.20858.
4. Rommer PS, Milo R, Han MH, et al. Immunological aspects of approved MS therapeutics. *Front Immunol*. 2019;10:1564. doi:10.3389/fimmu.2019.01564.
5. 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. doi:10.1056/NEJMoa044396.
6. 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. doi:10.1056/NEJMoa044397.
7. van Kempen ZL, Toorop AA, Sellebjerg F, et al. Extended dosing of monoclonal antibodies in multiple sclerosis. *Multiple Sclerosis Journal* 2021;2021:13524585211065711. doi:10.1177/13524585211065711.
8. Guery D, Marignier R, Durand-Dubief F, et al. Clinical failure of natalizumab in multiple sclerosis: Specific causes and strategy. *Rev Neurol (Paris)*. 2021;177:1241-1249. doi:10.1016/j.neurol.2021.02.393.
9. Trojano M, Ramio-Torrenta L, Grimaldi LM, et al. A randomized study of natalizumab dosing regimens for relapsing-remitting multiple sclerosis. *Mult Scler*. 2021;27:2240-2253. doi:10.1177/13524585211003020.
10. 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. doi:10.1002/jcph.707.
11. Shirani A, Stuve O. Natalizumab: Perspectives from the bench to bedside. *Cold Spring Harb Perspect Med*. 2018;8:a029066. doi:10.1101/cshperspect.a029066.
12. Salmen A, von Ahsen N, Trampe AK, et al. Longitudinal analyses of anti-JCV antibody index for risk assessment of progressive multifocal leukoencephalopathy. *Mult Scler J Exp Transl Clin*. 2016;2:2055217316630008. doi:10.1177/2055217316630008.
13. Ferro D, Prista-Leao B, Costa A, et al. Infectious risk mitigation in patients with multiple sclerosis under disease-modifying therapies - the experience of a collaborative neurology-infectious diseases approach. *J Cent Nerv Syst Dis*. 2021;13:11795735211042188. doi:10.1177/11795735211042188.
14. Hoepner R, Faissner S, Salmen A, et al. Efficacy and side effects of natalizumab therapy in patients with multiple sclerosis. *J Cent Nerv Syst Dis*. 2014;6:41-49. doi:10.4137/JCNSD.S14049.
15. Bernard-Valnet R, Koralnik IJ, Du Pasquier R. Advances in treatment of progressive multifocal leukoencephalopathy. *Ann Neurol*. 2021;90:865-873. doi:10.1002/ana.26198.
16. 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. doi:10.1016/S1474-4422(17)30282-X.
17. Berger JR, Fox RJ. Reassessing the risk of natalizumab-associated PML. *J Neurovirol*. 2016;22:533-535. doi:10.1007/s13365-016-0427-6.
18. Tugemann B, Berger JR. Improving risk-stratification of natalizumab-associated PML. *Ann Clin Transl Neurol*. 2021;8:696-703. doi:10.1002/acn3.51130.
19. Sellner J, Rommer PS. A review of the evidence for a natalizumab exit strategy for patients with multiple sclerosis. *Autoimmun Rev*. 2019;18:255-261. doi:10.1016/j.autrev.2018.09.012.
20. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2003;348:15-23. doi:10.1056/NEJMoa020696.
21. Rudick RA, Sandrock A. Natalizumab: Alpha 4-integrin antagonist selective adhesion molecule inhibitors for MS. *Expert Rev Neurother*. 2004;4:571-580. doi:10.1586/14737175.4.4.571.
22. Serra Lopez-Matencio JM, Perez Garcia Y, Meca-Lallana V, et al. Evaluation of natalizumab pharmacokinetics and pharmacodynamics: Toward individualized doses. *Front Neurol*. 2021;12:716548-722021. doi:10.3389/fneur.2021.716548.
23. Chang I, Muralidharan KK, Campbell N, et al. Modeling the efficacy of natalizumab in multiple sclerosis patients who switch from every-4-week dosing to extended-interval dosing. *J Clin Pharmacol*. 2021;61:339-348. doi:10.1002/jcph.1737.
24. Foley JF, Goelz S, Hoyt T, et al. Evaluation of natalizumab pharmacokinetics and pharmacodynamics with standard and extended interval dosing. *Mult Scler Relat Disord*. 2019;31:65-71. doi:10.1016/j.msard.2019.03.017.
25. Rothhammer V, Muschaweckh A, Gasteiger G, et al. alpha4-integrins control viral meningoencephalitis through differential recruitment of T helper cell subsets. *Acta Neuropathol Commun*. 2014;2:27. doi:10.1186/2051-5960-2-27.
26. https://www.ema.europa.eu/en/documents/product-information/tysabri-epar-product-information_en.pdf version of 04/05/2020.
27. Sehr T, Proschmann U, Thomas K, et al. New insights into the pharmacokinetics and pharmacodynamics of natalizumab treatment for patients with multiple sclerosis, obtained from clinical and in vitro studies. *J Neuroinflammation*. 2016;13:164. doi:10.1186/s12974-016-0635-2.
28. Wipfler P, Harrer A, Pilz G, et al. Natalizumab saturation: Biomarker for individual treatment holiday after natalizumab withdrawal? *Acta Neurol Scand*. 2014;129:e12-e15. doi:10.1111/ane.12182.
29. Zhovtis Ryerson L, Li X, Goldberg JD, et al. Pharmacodynamics of natalizumab extended interval dosing in MS. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:2020. doi:10.1212/NXI.0000000000000672.
30. 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. doi:10.1212/WNL.0000000000008243.
31. Clinicaltrials.org. *A study to evaluate efficacy, safety, and tolerability of EID of natalizumab (BG00002) in participants with RRMS switching from treatment with natalizumab SID in relation to continued SID treatment- followed by extension study comprising SC and IV natalizumab administration*; NCT03689972.
32. Foley JF, Defer G, Ryerson LZ, et al. Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): A randomised, controlled, open-label, phase 3b trial. *Lancet Neurol*. 2022;21:608-619. doi:10.1016/S1474-4422(22)00143-0.
33. 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. doi:10.1016/j.jns.2021.117385.
34. Bomprezzi R, Pawate S. Extended interval dosing of natalizumab: A two-center, 7-year experience. *Ther Adv Neurol Disord*. 2014;7:227-231. doi:10.1177/1756285614540224.
35. Chisari CG, Grimaldi LM, Salemi G, et al. Clinical effectiveness of different natalizumab interval dosing schedules in a large Italian population of patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2020;91:1297-1303. doi:10.1136/jnnp-2020-323472.
36. Butzkueven H, Kappos L, Spelman T, et al. No evidence for loss of natalizumab effectiveness with every-6-week dosing: A propensity score-matched comparison with every-4-week dosing in patients enrolled in the tysabri observational program (TOP). *Ther Adv Neurol Disord*. 2021;14:17562864211042458. doi:10.1177/17562864211042458.
37. Ryerson LZ, Naismith RT, Krupp LB, et al. No difference in radiologic outcomes for natalizumab patients treated with extended interval dosing compared with standard interval dosing: Real-world evidence from MS PATHS. *Mult Scler Relat Disord*. 2022;58:103480. doi:10.1016/j.msard.2021.103480.
38. Riancho JA. Does extended interval dosing natalizumab preserve effectiveness in multiple sclerosis? A 7 year-retrospective observational study. *Front Immunol*. 2021;12:614715.
39. Yamout BI, Sahraian MA, Ayoubi NE, et al. Efficacy and safety of natalizumab extended interval dosing. *Mult Scler Relat Disord*. 2018;24:113-116. doi:10.1016/j.msard.2018.06.015.
40. 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. doi:10.1136/jnnp-2019-322326.
41. Hoepner R, Kolb EM, Dahlhaus S, et al. Predictors of severity and functional outcome in natalizumab-associated progressive multifocal leukoencephalopathy. *Mult Scler*. 2017;23:830-835. doi:10.1177/1352458516667241.
42. Scarpazza C, De Rossi N, Tabiadon G, et al. Four cases of natalizumab-related PML: A less severe course in extended interval dosing? *Neurol Sci*. 2019;40:2119-2124. doi:10.1007/s10072-019-03959-4.
43. Bringeland GH, Myhr KM, Vedeler CA, et al. Wearing-off at the end of natalizumab dosing interval and risk of MS disease activity: A prospective 1-year follow-up study. *J Neurol Sci*. 2020;415:116880-122020. doi:10.1016/j.jns.2020.116880.
44. Bringeland GH, Blaser N, Myhr KM, et al. Wearing-off at the end of natalizumab dosing intervals is associated with low receptor occupancy. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:2020. doi:10.1212/NXI.0000000000000678.
45. van Kempen ZLE, Doesburg D, Dekker I, et al. The natalizumab wearing-off effect: End of natalizumab cycle, recurrence of MS symptoms. *Neurology*. 2019;93:e1579-e1586. doi:10.1212/WNL.0000000000008357.
46. Catherine D, Annelien P, Anne S, et al. End of dose interval symptoms in patients treated with natalizumab: A role for serum cytokines? *Mult Scler Relat Disord*. 2020;41:102020. doi:10.1016/j.msard.2020.102020.
47. Schwab N, Schneider-Hohendorf T, Posevitz V, et al. L-selectin is a possible biomarker for individual PML risk in natalizumab-treated MS patients. *Neurology*. 2013;81:865-871. doi:10.1212/WNL.0b013e3182a351fb.
48. Lieberman LA, Zeng W, Singh C, et al. CD62L is not a reliable biomarker for predicting PML risk in natalizumab-treated R-MS patients. *Neurology*. 2016;86:375-381. doi:10.1212/WNL.0000000000002314.
49. Schwab N, Schneider-Hohendorf T, Pignolet B, et al. Prospective validation of the PML risk biomarker l-selectin and influence of natalizumab extended intervals. *Neurology*. 2019;93:550-554. doi:10.1212/WNL.0000000000008135.

50. Punet-Ortiz J, Hervas-Garcia JV, Teniente-Serra A, et al. Monitoring CD49d receptor occupancy: A method to optimize and personalize natalizumab therapy in multiple sclerosis patients. *Cytometry B Clin Cytom*. 2018;94:327-333. doi:10.1002/cyto.b.21527.
51. Berkovich R, Togasaki DM, Cen SY, et al. CD4 cell response to interval therapy with natalizumab. *Ann Clin Transl Neurol*. 2015;2:570-574. doi:10.1002/acn3.190.
52. Zanghi 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. doi:10.1007/s13311-021-01037-2.
53. gov CT. *Personalized extended interval dosing of natalizumab in relapsing remitting multiple sclerosis*. NEXT-MS:NCT04225312.