



## Commentary

## Extended interval dosing of natalizumab: More evidence in support

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Natalizumab is a monoclonal antibody that antagonizes  $\alpha 4$ -integrin on circulating leukocytes, thereby inhibiting their trafficking into the central nervous system. It is a highly effective treatment for relapsing-remitting multiple sclerosis, and standard dosing is comprised of 300 mg natalizumab infusions every four weeks (standard-interval dosing, SID) [1]. Initial studies demonstrated leukocyte  $\alpha 4$ -integrin surface receptor saturation ( $>80\%$ ) with SID, and therapeutic adequacy supported by efficacy in the pivotal trials [2]. Shortly after approval, progressive multifocal leukoencephalopathy (PML) was recognized as a potential natalizumab-related complication, resulting in it being briefly pulled from the market. Subsequent work to define the incidence of natalizumab-related PML and its risk factors has been extensive. A French study from 2007 to 2016 found 2 cases of natalizumab-related PML per 1000 person years [3], but risk mitigation strategies such as John Cunningham virus (JCV) testing led to declining PML incidence after 2013.

Longer natalizumab treatment duration increases the risk of PML, prompting speculation that greater intervals between doses may partially mitigate PML risk. An early retrospective observational study based on the Tysabri Outreach: Unified Commitment to Health (TOUCH) database showed that extended interval dosing (EID), with a mean of 35–43 days between infusions, reduced PML risk by half compared to SID [4]. Subsequent pharmacologic studies demonstrated that individuals receiving SID maintain concentrations more than 10 times the 2  $\mu\text{g/mL}$  believed to be the minimal drug therapeutic level of natalizumab [5]. In a cross-sectional study of 214 patients receiving SID natalizumab, stepwise regression modeling was used to determine that infusions every six weeks (9 times yearly) was optimal dosing to maintain drug levels above 2  $\mu\text{g/mL}$  [5]. Dosing calculations, however, are complicated by the fact that drug concentrations and target receptor saturation correlate inversely with increasing body mass index (BMI) [5–7], and adjustment

of dosing interval by weight has been proposed as an extra step toward optimizing risks and benefits [5,7].

The NOVA study was a randomized, controlled, open-label trial meant to examine the safety and efficacy of EID. Clinically stable participants who had been receiving natalizumab for at least 12 months were randomized to remain on SID or switch to 6-week EID [8]. The primary endpoint was new or enlarging T2 lesions on MRI scans at 72 weeks, and there were significantly more in the EID group compared to the SID group. This result, though, was primarily driven by a single EID participant with 25 new lesions, many of which may have been related to the asymptomatic PML that this participant was eventually diagnosed with [9]. When the PML patient was excluded from the analysis, there were no meaningful differences in MRI brain outcomes between the two groups [10].

Prospectively collected data, as part of natalizumab monitoring or as part of collaborative research networks in MS, serve as an important resource for observational studies assessing the effectiveness and safety of EID in comparison to SID. A two-center North American study from 2014 (361 SID, 96 EID) showed similar relapse rates in those treated with SID in comparison to 6–8 week EID [11]. A later and larger study based on the Italian MS Register (1254 SID, 838 EID) with EID defined as 33–49 days (median 43 days) showed no difference for annualized relapse rate or disability progression at 12 and 24 month follow-ups [12], while a study based on the international Tysabri Observational Program (219 propensity-matched), with EID defined as 6 weeks, also showed no difference for annualized relapse rate or cumulative probability of 6-month disability worsening [13]. The latter study noted 2 cases of PML in the EID group, but none in SID [13]. A study based on Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS) data assessing quantitative MRI outcomes in SID ( $<35$  days) vs. EID ( $>35$

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days) showed no differences for annualized percentage change in T2 lesion volume and brain parenchymal fraction [14].

This issue of *Neurotherapeutics* features a study by Ruggieri et al. that expands on previous observational studies of EID [15]. The authors conducted a retrospective analysis of a cohort from 8 Italian centers. The primary aim was to compare outcomes among those receiving SID versus those receiving EID (defined as >5 weeks–7 weeks). In a secondary analysis, EID was defined as >7 weeks–8 weeks. An exploratory analysis evaluating the impact of BMI on outcomes in SID and EID groups was also conducted. The primary outcome was evidence of disease activity (EDA), defined as clinical relapses, MRI activity, or disability worsening per the Expanded Disability Status Scale (EDSS). Un-adjusted, adjusted (sex, age, disease duration, previous treatment, baseline EDSS, baseline MRI activity, number of relapses during 2 previous years), and (inverse probability treatment) weighted approaches were applied to time-to-event analyses.

The cohort included 745 adults with a mean follow-up of 3.3 years. Most participants were female (>65%) with an average disease duration of 8.5 years. A majority had received previous disease-modifying therapy (>80%), and those starting an SID natalizumab regimen had more relapses in the 2 preceding years.

In the primary analysis, there were no differences between SID and EID (5–7 weeks) for the specified outcomes. Similar results were seen for SID vs. EID (7–8 weeks), but the authors noted a trend toward greater hazard for clinical relapses with EID (HR 1.74, 95% CI 0.99–3.02,  $p = 0.054$ ). In the exploratory BMI analysis, there was a significant interaction between BMI and treatment regimen with respect to EDA, suggesting that BMI is a relevant factor when choosing a dosing regimen. This applied both when BMI was treated as continuous or binarized as above or below the median (23.74 kg/m<sup>2</sup>). Notably, no differences in EDA were seen between the binarized BMI groups when the inverse probability treatment weighted models were applied.

The study from Ruggieri et al. has several strengths: a robust sample size, mean follow-up of >3 years, MRI acquisition protocols adhering to shared standards (MAGNIMS guidelines for MS treatment monitoring), and central computing of natalizumab dosing. Several analytical approaches were applied to increase robustness of the analysis and affirm the results and interpretation. However, selection bias is an important limitation inherent to the chosen methodology. As the authors acknowledge, higher baseline levels of disease activity were present in the SID group. Although these discrepancies were adjusted for statistically, caution is necessary when applying the results to patients with more active disease. Most participants received prior treatment, and carry-over or additive effects are possible. Also, natalizumab serum levels or target receptor saturation levels were unavailable as covariates, both of which have previously been shown to be relevant when studying the effects of BMI on natalizumab therapeutic effectiveness. Finally, the cohort was exclusively Italian, and predominantly comprised of individuals with a normal BMI, which limits generalizability of the finding, especially for North American populations in which obesity is more common.

Overall, the main findings of the study by Ruggieri et al. are in line with previous observational studies demonstrating similar benefits with EID versus SID at a dosing interval of 6 weeks. This supports the notion of being able to extend the natalizumab dosing interval without compromising expected benefits, and potentially reducing harm of PML. Reductions in infusion frequency also have the benefits of decreasing cost and increasing patient convenience. Nevertheless, EID natalizumab has not been studied as a first line approach, and most participants in the current study were on previous treatments. Additional data are needed in patients with more recently diagnosed, and likely more active, disease. Although the exploratory BMI analysis is a valuable addition to the literature, further studies are needed, ideally including parallel information on natalizumab concentrations and target receptor saturation. An ongoing prospective Dutch study is poised to provide further high-quality evidence regarding the feasibility, risks, and benefits of personalized EID

of natalizumab based on drug concentrations (NCT04225312) [16]. An initial analysis reporting outcomes for 376 participants showed adequate disease control with personalized dosing based on target trough levels (10 µg/mL or 5 µg/mL) being comparable to the SID arm and historical SID data [16]. Finally, the true impact of EID on PML risk is challenging to assess due to the relative rarity of natalizumab associated PML. Continued monitoring of the TOUCH database and other large registries is needed to further elucidate the risk reduction provided by EID.

## Author Contributions

Karlo Toljan: Writing and editing.

Devon S Conway: Writing and editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Devon Conway reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory and funding grants. Devon Conway reports a relationship with Biogen Inc that includes: funding grants and speaking and lecture fees. Karlo Toljan reports a relationship with National Multiple Sclerosis Society that includes: funding grants. Devon Conway reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory and funding grants. Devon Conway reports a relationship with Horizon Therapeutics USA Inc that includes: funding grants. Devon Conway reports a relationship with Alexion that includes: consulting or advisory. Devon Conway reports a relationship with EMD Serono Inc that includes: funding grants. Devon Conway reports a relationship with US Department of Defense that includes: funding grants. Devon Conway reports a relationship with TG Therapeutics Inc that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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