

Natalizumab wearing-off effect

The hunt for the elusive pharmacodynamic biomarker

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Natalizumab is a highly efficacious humanized recombinant antibody against $\alpha 4$ -integrin that is approved for relapsing forms of MS.¹ Regular natalizumab dosing is 300 mg IV every 4 weeks. Roughly one-third of the patients report a wearing-off effect of natalizumab, generally in the last week of their infusion cycle. Wearing-off is predominantly manifest by fatigue and neurogenic pain. Changes in the neurologic examination are infrequent, and a correlation with MRI worsening has not been reported.

Given that natalizumab works by blocking leukocyte access to the brain and spinal cord, a dose effect and consequently a wearing-off phenomenon appear biologically plausible. Very likely, there is a threshold effect for natalizumab efficacy and safety. Higher body weight has previously been shown to correlate with lower receptor occupancy (RO).² The advent of extended interval dosing (EID) for progressive multifocal leukoencephalopathy mitigation has amplified the importance of understanding the relationship between natalizumab efficacy and the wearing-off phenomenon.³

In this issue of *Neurology*[®]: *Neuroimmunology & Neuroinflammation*, Bringeland et al.⁴ categorized patients with relapsing-remitting MS (RMMS) based on their reported wearing-off effect (regular, sometimes, never) and used mass cytometry to compare their natalizumab RO. Specifically, 40 RRMS participants were enrolled in a single center cross-sectional study. Clinical and demographic data including disease characteristics, treatment duration, wearing-off symptoms, age, body mass index (BMI), working status, smoking habits, and vitamin D levels were analyzed. Eight patients (20.0%) reported regular occurrence of wearing-off symptoms; of interest, these individuals had lower natalizumab RO than patients who reported having such symptoms sometimes or never. A higher BMI was associated with a lower RO. No other demographic or disease characteristics were associated with the wearing-off phenomenon.

Other investigators failed to show a similar association between $\alpha 4$ -integrin RO (saturation) and wearing-off symptoms. In a study by van Kempen et al., a total of 32% of 93 patients on natalizumab reported current symptoms of wearing-off, with 54% reporting wearing-off symptoms at some point. Surprisingly, the wearing-off effect was more frequently reported in a standard interval group (SID) (39%) than in an extended interval group (19%). In addition, the wearing-off effect was not associated with numerous variables, including body weight.

It is challenging to ascertain why these studies from Bringeland et al.⁴ and van Kempen et al.³ came to different conclusions regarding the wearing-off phenomena. Although both used validated and custom patient-reported outcomes (PROs) to define wearing-off, the tools used had no commonality. It is conceivable that the use of separate instruments contributed to patient-reported differences in the definition and duration of the wearing-off effect. The timing of PRO administration is not defined in the Bringeland cohort and therefore could be sampling patient experience at differing intervals relative to their infusion.

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Wearing-off at the end of natalizumab dosing intervals is associated with low receptor occupancy

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Although Bringeland did not study an EID population, the fact that a higher percentage of wearing-off was seen in the van Kempen SID cohort would make the association between lower RO and wearing-off less likely. An intermediate effect on RO in the Bringeland “sometimes” patient group was also not seen. The small sample size in the Bringeland “regular” group may also be playing a role in these observations. The correlation between lower RO and higher weight groups has been extensively delineated. BMI does tend to follow weight with a similar effect, and hence, higher BMI patients would be expected to have lower RO.

Methodological issues may also explain the differences in study outcomes between the 2 studies, namely, multiparameter flow vs mass cytometric assays that were used. It appears that van Kempen et al.³ assessed natalizumab binding to α 4-integrin exclusively on CD8 effector memory and effector cells. In their study, experimental samples were compared with saturated reference sample. By contrast, Bringeland et al.⁴ stained all peripheral blood leukocytes. Then, bound natalizumab was detected with an anti-IgG4 antibody, and total α 4-integrin was detected with an anti-CD49d antibody specific for a different epitope than natalizumab. Indeed, Bringeland et al.⁴ did determine that wearing-off symptoms were associated with reduced RO in CD4⁺ and CD8⁺ T cell subsets before infusion. Both cell types are thought to perpetuate MS disease activity through local proinflammatory effects within the CNS,^{5–7} and both cell types are diminished in the capability to travel to the CNS by natalizumab.⁸

As stated above, natalizumab is a highly effective therapy for patients with active MS. In our opinion, it is unlikely that a standard dosing interval of natalizumab will provide optimal benefits for all recipients. Although the wearing-off effect does

not clearly correlate with declining efficacy as defined by increased relapses or MRI associated change, further study to solidify the relationship between the wearing-off phenomenon and pharmacodynamic and pharmacokinetic markers is certainly warranted. The efficacy of EID is currently being evaluated in a clinical trial (clinicaltrials.gov/ct2/show/NCT03689972). Ultimately, cellular or molecular biomarkers will be necessary to define the optimal natalizumab dose in individual patients.

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Disclosure

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