Prospective trial of natalizumab personalised extended interval dosing by therapeutic drug monitoring in relapsing-remitting multiple sclerosis (NEXT-MS)

Marcus Koch

Natalizumab treatment in relapsing-remitting multiple sclerosis: can we safely personalise treatment intervals?

In *JNNP*, Toorop and coworkers present the results of the NEXT-MS trial, a clinical trial on individualised extended interval dosing (EID) of natalizumab (NTZ) in people with relapsing-remitting multiple sclerosis (RRMS).[1]

NTZ was one of the first high-efficacy treatments in RRMS, and has remained popular since its introduction in the late 2000s. NTZ is typically administered at a dose of 300 mg every 4 weeks. The two pivotal phase 3 NTZ trials, AFFIRM[2] and SENTINEL[3] were published back-to-back in the New England Journal in 2006, and while the AFFIRM trial reported no unexpected adverse events, two SENTINEL participants developed progressive multifocal leucoencephalopathy (PML), a very serious and often deadly opportunistic infection of the central nervous system. In the years since, many more cases of PML have occurred in people treated with NTZ, which made it possible to identify risk factors and employ risk stratification strategies. Since the number of NTZ treatments is a risk factor for developing PML, one strategy to mitigate PML risk is to reduce the exposure to NTZ by EID. The recent NOVA trial, published 16 years after the original phase 3 trials, suggested that the dosing interval can be safely extended to 6 weeks.[4]

The NEXT-MS trial is a further refinement of this EID strategy. NEXT-MS is an investigator-initiated non-inferiority trial involving 21 sites in the Netherlands. In NEXT-MS, the interval to the next NTZ infusion was chosen based on serum NTZ trough levels measured throughout the trial. The primary outcome in NEXT-MS was radiological disease activity (new or newly enlarging T2 lesions on cranial MRI), and the main comparison was between participants with a target trough NTZ concentration of 10 µg/mL (EID10, n=251) and a historical control group of patients receiving standard, every 4 weeks, dosing (historical standard interval dosing, HSID, n=87). Using the NEXT-MS algorithm, 82% of participants were able to extend their dosing interval beyond 4 weeks. After a median follow-up of 86.9 weeks, the incidence rate of radiological disease activity was 10.0 per 1000 person-years in the EID10 group, compared with 24.7 per 1000 person years in the HSID group, which suggests that EID based on a 10 µg/mL trough level cut-off is non-inferior to SID. An exploratory analysis in NEXT-MS furthermore suggests that EID based on a 5 µg/mL trough level cut-off may also be feasible. In addition to recording radiological disease activity, NEXT-MS compared physical disability (using the Expanded Disability Status Scale), relapse frequency, serum neurofilament light chain concentrations and the development of seropositivity for JC virus, all of which comparisons showed no disadvantages of EID. No PML cases occurred. Encouraged by this success, the NEXT-MS investigators decided to continue the study with an amended protocol to investigate EID intervals of 6 or more weeks, based on a trough level of 5 mg/mL.

The NEXT-MS results show that personalised EID using NTZ trough levels is feasible. Its introduction into clinical practice will reduce treatment burden and cost, and likely also improve treatment safety.

Correspondence to Dr Marcus Koch, Clinical Neurosciences, University of Calgary, Calgary, AB T2N 1N4, Canada; mwkoch@ucalgary.ca

Contributors MK conceived of and wrote this commentary as the sole author.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Koch M. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2023-332758

Received 26 October 2023
Accepted 29 October 2023

► http://dx.doi.org/10.1136/jnnp-2023-332119

J Neurol Neurosurg Psychiatry 2023;**0**:1. doi:10.1136/jnnp-2023-332758

ORCID iD
Marcus Koch http://orcid.org/0000-0001-9972-5092

REFERENCES

1 Toorop AA, van LieropZ, Gelissen LMY, *et al*. Prospective trial of Natalizumab personalized extended interval dosing by therapeutic drug monitoring in relapsing-remitting multiple sclerosis (NEXT-MS). *J Neurol Neurosurg Psychiatry* 2023.
2 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.
3 Rudick RA, Stuart WH, Calabresi PA, *et al*. Natalizumab plus interferon Beta-1A for relapsing multiple sclerosis. *N Engl J Med* 2006;354:911–23.
4 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;21:608–19.