Short report

Decrease of natalizumab drug levels after switching from intravenous to subcutaneous administration in patients with multiple sclerosis

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ABSTRACT

Background Natalizumab is effective in the treatment of multiple sclerosis (MS). In 2021, the European Medicines Agency approved the subcutaneous (SC) variant of natalizumab which can be used instead of intravenous administration. However, the course of drug levels varies between administration routes, and the Food and Drug Administration rejected the request for approval of natalizumab SC for reasons that were not disclosed. Our objective was to evaluate the course of natalizumab trough drug levels in patients who switched from natalizumab intravenous to SC on various treatment intervals.

Methods The NEXT-MS trial (N=382) investigates personalised treatment of natalizumab, in which infusion intervals are prolonged based on individual natalizumab trough drug levels. In 2021, an amendment was approved allowing participants to switch from intravenous to SC administration with frequent measurements of natalizumab drug levels and antidrug antibodies (ADAs). Results were compared with linear mixed model analyses.

Results Until December 2022, 15 participants switched to SC natalizumab. Natalizumab drug levels with SC administration were on average 55% lower compared with intravenous administration (Exp (estimate) 0.45, 95% CI 0.39 to 0.53, p<0.001), leading to very low trough drug levels in three patients on extended treatment intervals. No natalizumab ADAs were detected during intravenous or SC treatment. None of the participants on natalizumab SC showed evidence of MS disease activity.

Conclusions Natalizumab trough drug levels can decrease after switching from natalizumab intravenous to SC administration. We advise to monitor trough drug levels in patients with low natalizumab drug levels during intravenous treatment, patients with higher body mass index or patients on extended treatment intervals who switch to SC administration of natalizumab.

INTRODUCTION

Natalizumab, a monoclonal antibody used in relapsing remitting multiple sclerosis (MS), reduces inflammation within the central nervous system by preventing migration of lymphocytes across the blood–brain barrier.1 In 2006, intravenous natalizumab was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in a treatment regimen of 300 mg every 4 weeks. With intravenous administration, natalizumab trough levels are highly variable between patients, while intraindividual trough levels are usually stable.2 In 2021, the EMA approved the subcutaneous (SC) variant of natalizumab (300 mg every 4 weeks). Trough drug levels prior to redosing were similar between intravenous and SC natalizumab in the DELIVER trial.3 However, the course of serum natalizumab drug levels, and consequently receptor saturation on lymphocytes, may differ between intravenous and SC administration.7 The FDA rejected the request for approval of natalizumab SC for reasons that were not disclosed but could be related to insufficient data on pharmacokinetics.

In recent years, extended interval dosing of natalizumab, in which the treatment interval of 4 weeks is prolonged, has gained popularity as this leads to a decreased risk of progressive multifocal leukoencephalopathy.4 Both retrospective5 6 and prospective7 8 studies showed similar efficacy between natalizumab standard interval dosing (4 weeks interval) and extended interval dosing (5–8 weeks interval). When applying extended dosing, it is of importance that natalizumab trough drug levels are maintained above approximately 1–2 µg/mL, as α4-integrin receptor desaturation can occur when trough drug levels fall below 1–2 µg/mL, which can lead to rebound disease activity.9 10 In the PDNMS trial, natalizumab treatment intervals were personalised based on individual natalizumab trough drug levels in 61 patients.8 In the ongoing follow-up study, the NEXT-MS trial (ClinicalTrials.gov identifier NCT04225312), personalised treatment of natalizumab is studied in a larger group. Since the approval of SC natalizumab, participants in the NEXT-MS trial can switch from natalizumab intravenous to SC administration.

As there is insufficient data regarding the influence of natalizumab SC on drug levels when switching from intravenous to SC administration,
especially in extended dosing, we share preliminary data on pharmacokinetics of participants of the NEXT-MS trial who switched from intravenous to SC administration of natalizumab.

**METHODS**

**Study protocol**

The NEXT-MS trial is an ongoing investigator-initiated multicentre prospective open-label non-randomised trial (ClinicalTrials.gov identifier NCT04225312) studying personalised intravenous natalizumab treatment (300 mg) in which infusion intervals are adjusted based on individual natalizumab trough drug levels. Patients can participate in three groups: standard interval dosing, extended interval dosing with an aim trough concentration of 10 µg/mL (EID10), and extended interval dosing with a lower aim trough concentration of 5 µg/mL (EID5). Adult patients with MS who received ≥6 natalizumab infusions are included. Trough drug levels are monitored every 1–6 months during extended dosing (more frequent during start (EID5). Adult patients with MS who received ≥6 natalizumab infusions are included. Trough drug levels are monitored every 1–6 months during extended dosing (more frequent during start of personalised dosing). Treatment intervals are shortened when trough drug levels are <2 µg/mL. In June 2021, an amendment was approved allowing participants to switch to natalizumab SC (300 mg) on their current treatment interval with measurements of natalizumab trough drug levels prior to every injection and natalizumab antidrug antibodies (ADAs) after switching from intravenous to SC. Natalizumab SC was administered by trained healthcare professionals within the participating hospitals of the NEXT-MS trial. Administration was recorded in the electronic patient files. All participants who switched to natalizumab SC until December 2022 with a minimum of one available follow-up blood sample after the switch are described here. Blood samples were analysed centrally at Sanquin Laboratory Amsterdam for measurement of natalizumab drug concentrations and ADA. A cross-linking assay using polyclonal rabbit antinatalizumab fragments and mouse anti-IgG, monoclonal antibodies for detection were used as previously reported.11

**Statistical analyses**

Descriptive data are presented as means with SD, medians with IQR or frequencies with percentages. Natalizumab trough drug levels during intravenous and SC administration were compared using linear mixed effect models, with fixed effect for administration and treatment interval, and random effect for subjects. Ln-transformation was applied to natalizumab drug levels. All statistical analyses were conducted with SPSS statistic software V.28.0 (IBM). Figures were designed in GraphPad Prism V.9.3.1 for Windows (GraphPad software, San Diego, California USA). A p<0.05 was considered statistically significant.

**RESULTS**

**Baseline characteristics**

Until December 2022, 382 patients were included in the NEXT-MS trial of whom 317 received personalised treatment. Fifteen participants switched from natalizumab intravenous to SC administration with a minimum of one available follow-up blood sample. The main reason for switching to SC administration was difficulty with obtaining intravenous access. Median duration of follow-up after switching to SC administration until last blood sample collection or last available MRI was 6.9 months (IQR 5.0–10.4 months). Patient characteristics and data on natalizumab trough drug levels are described in table 1 and figure 1.

**Natalizumab trough drug levels, ADAs and MS disease activity after switching to natalizumab SC**

Natalizumab trough drug levels of 12 out of 15 participants switching from natalizumab intravenous to SC were lower after switching (case 1–5, 7–9, 11, 13–15), resulting in a shorter treatment interval in three participants (case 1, 3 and 4) when trough drug levels were <2 µg/mL (figure 1). When

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**Table 1 Patient characteristics, study groups and natalizumab ADAs**

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<tr>
<th>Case</th>
<th>BMI (kg/m²)</th>
<th>Duration intravenous treatment (mo)</th>
<th>Duration in study (mo)</th>
<th>Study group</th>
<th>Duration SC treatment (mo)</th>
<th>Duration of radiological FU (mo)</th>
<th>NTZ ADA (intravenous)</th>
<th>NTZ ADA (SC)</th>
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BMI was recorded at baseline of the NEXT-MS trial. Duration intravenous treatment and duration in NEXT-MS trial were calculated until switching to SC administration. Duration of SC treatment was calculated between start of SC treatment and last blood sample collection or last available MRI scan after switching to SC administration. Duration of radiological FU was calculated between start of natalizumab SC and the last available MRI scan after switching to SC administration (median FU 6.9 months, IQR 5.0–10.4 months). Natalizumab ADAs (AE/mL) during intravenous treatment were measured once at baseline of the NEXT-MS trial. Natalizumab ADAs during SC treatment were measured prior to SC administration.

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Multiple sclerosis

Figure 1  Natalizumab trough drug levels (µg/mL) under intravenous and SC administration per participant. Boxplots represent median natalizumab trough drug levels with minimum and maximum concentrations (1–9 samples per boxplot). Colours represent treatment intervals during natalizumab treatment before and after switching to natalizumab SC. Treatment intervals during administration were extended after two measurements on standard interval dosing according to the NEXT-MS trial protocol. Natalizumab concentrations were lower in 12/15 participants after the switch (case 1–5, 7–9, 11, 13–15). *Adjusted treatment intervals (protocol deviations): case 2: preferred 5 weeks interval during SC treatment and one-time 6 weeks interval due to patient factors; case 3: two-time 7 weeks interval (urinary tract infection and patient factors) and one-time 5 weeks interval due to patient factors with very low drug levels (<0.2 µg/mL) with a shortened treatment interval to 4 weeks and 5 weeks thereafter according to the NEXT-MS trial protocol; case 6: three-time 5 weeks interval due to patient factors, illness and herpes labialis; case 7: preferred 4 weeks interval during SC treatment and one-time 5 weeks interval due to patient factors. MS, multiple sclerosis; SC, subcutaneous.

comparing natalizumab trough drug levels between intravenous and SC administration, with treatment interval included as a covariate, natalizumab drug levels with SC administration were on average 55% lower compared with intravenous administration (Exp (estimate) 0.45, 95% CI 0.39 to 0.53, p<0.001). No natalizumab ADAs were detected in any of the participants on natalizumab SC. So far, none of the participants on natalizumab SC showed evidence of radiological or clinical disease activity (table 1).

DISCUSSION

In our study, trough drug levels of natalizumab decreased after switching to SC administration with a similar dose of 300 mg, leading to very low trough drug levels in three patients. As most natalizumab-treated patients still have high drug levels prior to redosing,4 switching to SC administration will not lead to subtherapeutic natalizumab levels in the majority of patients. However, in patients with low natalizumab trough drug levels during intravenous treatment, patients on extended treatment intervals, or patients with higher body mass index (BMI) as higher BMI is associated with lower drug concentrations,12 a switch from intravenous to SC administration could lead to subtherapeutic natalizumab concentrations and could possibly lead to rebound disease activity.

So far, none of the participants on natalizumab SC in our study showed evidence of radiological or clinical disease activity. In compliance with the study protocol of the NEXT-MS trial, treatment intervals were shortened in our cohort when trough drug levels fell below 2 µg/mL. (cases 1, 3 and 4). It was therefore expected that there was no return of disease activity, as adequate α4-integrin receptor saturation is preserved when the treatment interval is adjusted based on trough drug levels.10

So far, data on pharmacokinetics of natalizumab SC is described in two trials.3 13 The DELIVER trial studied natalizumab pharmacokinetics and pharmacodynamics of intramuscular, SC and intravenous administration of natalizumab every 4 weeks in natalizumab-naive patients.4 In this trial, the
bioavailability of natalizumab SC was 57%–71% compared with intravenous administration with lower peak serum drug levels (40%).

Trough drug levels were 19–40 µg/mL after intravenous administration and 13–34 µg/mL after SC administration. The REFINE trial studied clinically stable patients with relapsing remitting MS switching from intravenous to SC administration of either 300 mg every 4 or 12 weeks, or 150 mg every 4 or 12 weeks. Similar natalizumab trough drug concentrations between SC and intravenous administration were reported with treatment every 4 weeks. However, in both the DELIVER and REFINE trial, natalizumab trough levels were only reported on a group level and not compared intraintidually when switching from intravenous to SC (REFINE trial). Furthermore, in the figures presented in both trials, there seems to be a trend towards lower drug concentrations in the SC study groups compared with the intravenous study groups. As the FDA has rejected the request for approval of natalizumab SC, it would be of interest if more data on pharmacokinetics of both studies were disclosed. Currently, another prospective trial on natalizumab SC in standard and extended treatment intervals is ongoing (ClinicalTrials.gov NCT04225312). Hopefully, extensive data on pharmacokinetics and pharmacodynamics will be shared to further clarify the efficacy of SC natalizumab.

Strengths of this study include longitudinal measurements of natalizumab trough drug levels and ADA of individual patients on standard and extended treatment intervals after switching to natalizumab SC in a prospective clinical trial setting. Limitations include intraintidual variations in treatment intervals, short follow-up and low number of cases.

In conclusion, in our cohort of 15 patients switching from intravenous to SC administration, natalizumab trough drug levels decreased in 12 patients. We advise to monitor trough drug levels in patients with low natalizumab drug levels during intravenous treatment, patients with higher BMI or patients on extended treatment intervals who switch to SC administration. Additional longitudinal pharmacokinetic data of SC natalizumab in standard and extended interval dosing regimens are essential.
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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by VUMC Ethics committee number 2019.552. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Research data will be shared anonymously on request from any qualified investigator.

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Supplementary appendix

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