Personalized extended interval dosing of natalizumab in relapsing remitting multiple sclerosis

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This study has been transitioned to CTIS with ID 2024-513105-31-00 check the CTIS register for the current data. Primary Objective: Our objective is to validate the safety, measured by radiological disease activity, of personalized extended interval...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Demyelinating disorders
Study type	Interventional

Summary

ID

NL-OMON54545

Source
ToetsingOnline

Brief title
NEXT-MS

Condition

- Demyelinating disorders

Synonym
Multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Innovatiefonds Zorgverzekeraars;Stichting MS Research;de Hersenstichting;stichting Treatmeds

Intervention

Keyword: Extended interval dosing, Multiple sclerosis, Natalizumab

Outcome measures

Primary outcome

Our primary endpoint is radiological disease activity (new/enlarging T2 lesions on brain MRI) after two years.

Secondary outcome

1) Percentage of patients preferring personalized treatment over standard treatment and percentage staying on personalized treatment

2) Cost analysis and annual cost reduction

3) Annual JC virus conversion rate comparing the PEID group with the control group and historic control group

4) Course JC virus index in JC+ patients comparing the PEID group with the control group

5) Quality of life on the MSIS-29 comparing the PEID group with the control group

6) Satisfaction of treatment on the TSQM comparing the PEID group with the control group

7) The occurrence of the natalizumab wearing-off effect comparing the PEID group with the control group

8) Annual relapses comparing the PEID group with the historic control group and control group

9) Disability progression (EDSS) comparing the PEID group with the historic control group and control group

10) Brain atrophy as measured with MRI comparing the PEID group with the historic control group and control group

11) Long-term stability of natalizumab trough concentration in personalized interval dosing with intravenous and subcutaneous administration

12) Incidence of progressive multifocal leukoencephalopathy

13) Difference in serum neurofilament light levels with personalized interval dosing

Study description

Background summary

Natalizumab, is effective in the treatment of relapsing remitting multiple sclerosis (RRMS). Based on the different therapeutic dosages of 3-6 mg/kg in phase II trials, a fixed dose of 300mg of natalizumab once every four weeks was chosen for phase III trials in order that the majority of patients (with weights ranging between 50 and 100kg) would fall between a dose of 3-6 mg/kg. In 2006, a dose of 300mg every four weeks was approved by the EMA/FDA for the treatment of RRMS. However, in this treatment regimen, natalizumab concentrations may stay detectable in serum up to 200 days after cessation of therapy.

Natalizumab binds to the α4 subunit of the α4ß1-integrin (VLA-4) receptor on lymphocytes. Adhesion of the VLA-4 receptor with its ligand, the vascular cell adhesion molecule-1 (VCAM-1) receptor on endothelial cells, mediates migration of lymphocytes across the blood brain barrier. Natalizumab blocks this pathway and hereby halts lymphocyte driven inflammatory demyelination within the central nervous system.
Saturation of the α4-integrin receptor is associated with the natalizumab concentration, which can be measured by ELISA in serum. The natalizumab concentration peaks directly after infusion, after which an exponential decay sets in. Significant disease activity returns when the receptor saturation falls under 20% and receptor desaturation (defined as <50%) occurs when the natalizumab concentration falls under 1-2.5µg/ml. After a standard 4-week treatment interval, the natalizumab nadir concentration varies widely between patients, ranging from 0.1-80µg/ml. However, the mean natalizumab nadir concentration (25µg/ml), lies far above the therapeutic threshold, which implies the large majority of patients has an excess of natalizumab at time of

re-dosing.

The major disadvantage of natalizumab is the risk of developing progressive multifocal leukoencephalopathy (PML). PML is an opportunistic demyelinating and possibly lethal brain infection caused by the John Cunningham (JC) virus. Approximately, 55% of de Dutch population is positive for the JC virus, with 1-2% JC seroconversion annually. Unfortunately, the seroconversion rate in MS patients treated with natalizumab appears to be substantially higher, which remains poorly understood. Because of PML risk many JC virus positive patients using natalizumab over 2 years have been forced to stop this effective therapy. However, very recent evidence is showing a drastic decrease of the risk of PML in patients with extended natalizumab infusion intervals.

After one year of treatment, intra-individual natalizumab nadir concentrations stay stable in a set treatment interval, which makes this a suitable marker for extending the treatment interval. A natalizumab nadir concentration of >10µg/ml is considered high, and is a safe cut-off for extending infusion intervals in those patients with high natalizumab nadir concentrations. Approximately 85-95% of patients have natalizumab nadir concentrations above 10µg/ml.
As receptor desaturation (<50%) occurs when the natalizumab concentration falls under 1-2.5µg/ml and significant disease activity seems to return when receptor saturation falls under 20%, it seems plausible that the interval could be safely extended to a natalizumab nadir concentration of 5µg/ml.

As of April 2021, the European Commission has granted marketing authorization for subcutaneous (SC) injection of natalizumab. SC administration was studied in 2 clinical trials (DELIVER (NCT00559702) and REFINE (NCT01405820)) where SC administration showed comparable efficacy and safety to IV administration of natalizumab (Plavina et al. 2016; Trojano M. et al. presented at AAN Annual Meeting). Pharmacokinetic- and pharmacodynamics model-based simulations resulted in comparable trough natalizumab serum concentration and α4-integrin receptor saturation between SC and IV administration at a dose of 300 mg every 4 weeks (Zhao Y, et al. ACTRIMS 2021 virtual forum, P024).

In 2015, we started a Dutch multi-center trial (the PDNMS trial) with personalized extended interval dosing (PEID) of natalizumab based on trough concentrations in patients who did not show disease activity under natalizumab the year prior to inclusion (no relapses, no new/enlarging T2 lesions or gadolinium enhancing lesions on MRI). Sixty-one patients were included. The aim was a natalizumab trough concentration of 10µg/ml. Natalizumab trough concentration was measured before every infusion and the infusion interval was prolonged when the concentrations >=15µg/ml in two consecutive infusions with the same interval. Study follow-up was one year with an extension phase of one year. Patients received a 3 monthly follow-up with a clinical evaluation and an MRI brain scan (including gadolinium enhanced sequences). All patients remained without disease activity (clinically and radiologically) during the first year of PEID, proving our hypothesis that efficacy of natalizumab does not decrease

with PEID. Furthermore, all patients who completed the extension phase (n=22) did not show any disease activity.

In 2020, the first patient was included in the NEXT-MS study, in which patients received PEID with an aim trough concentration of 10 µg/mL in the main group and 5 µg/mL in a subgroup. Results of our interim analyses showed comparable disease activity between patients in the main group, the subgroup and the control group (4-weekly infusions). The subgroup enabled participants to extend time between infusions safely to 6.3 weeks (range 4-9). Furthermore, The NOVA study was an international study that randomized patients between 4 and 6 week natalizumab dosing intervals with a primary outcome measure of new or enlarging T2 lesions during 72 weeks of follow-up. The results showed that natalizumab administered every 6 weeks provides a high level of efficacy after 72 weeks in stable RRMS patients who switched from the 4 week interval (Foley et al. 2022). Although the primary outcome (estimated mean number of new/enlarged T2 lesions) was higher in the 6 weeks group (0.20 [0.07 to 0.63] vs. 0.05 [0.01 to 0.22]), this difference was evaluated as not clinically meaningful, since the lesions were detected in 1 patient who discontinued natalizumab for 3 months and 1 patient who developed PML. There were no differences in annualized relapse rate or new T1 hypointense lesions, and safety profile of natalizumab was similar between the groups. In addition, recent studies showed a drastic decrease of the risk of PML in natalizumab patients who received extended interval dosing (EID).*

Personalized extended interval dosing with natalizumab serves multiple purposes. Firstly, it puts the patients* individual biological needs centrally and decreases overuse of natalizumab, increasing efficient use of healthcare and expensive medication. Secondly, with extending infusion intervals the disease burden of the patient decreases with fewer hospital visits. And thirdly, the risk of PML is decreased with extending natalizumab infusion intervals.

Study objective

This study has been transitioned to CTIS with ID 2024-513105-31-00 check the CTIS register for the current data.

Primary Objective:
Our objective is to validate the safety, measured by radiological disease activity, of personalized extended interval dosing of natalizumab to >=6 weeks (with an aim natalizumab trough concentration of 5 µg/ml) in a large real-life cohort across the Netherlands. Our objective is to follow at least 184 patients on PEID for 2 years. Finally, we hope to provide sufficient data to implement our strategy as standard natalizumab care in Dutch MS treatment guidelines.

Secondary Objectives:
- Determining clinical disease activity and disability progression in extended

patients
- Providing a cost analysis of PEID.
- To assess the influence of PEID on JC virus conversion, JC virus index, incidence of progressive multifocal leukoencephalopathy.
-To determine treatment satisfaction and quality of life in this large real-life setting cohort.
-To study the long-term stability of natalizumab trough concentration and the prevalence of natalizumab antibodies in the standard 4 week interval.

Study design

The proposed trial is a national open label phase IV natalizumab cohort study trial. Our aim is that the large majority of natalizumab treated RRMS patients who are currently treated with PEID in the Netherlands will continue in this study.We will continue the study with 24 participating centers. The study duration is 96 weeks. This study will contain the PEID group, a control group, and a historic control group. If patients desire a personalized natalizumab treatment and have been treated with >=6 consecutive natalizumab infusions, they have the opportunity of entering the study as a participant of the PEID study group. Participants with a current treatment schedule of every 4 or 5 weeks will have one measurement of natalizumab concentration in the current interval. Participants will then directly switch to a treatment schedule of every 6 weeks. Participants with a current treatment schedule of >=6 weeks will have one measurement of natalizumab concentration in the current interval. Participants will then possibly further extend the treatment interval based on the natalizumab concentration. The PEID study group will receive a personalized treatment with an interval of >=6 weeks. If patients do not desire a personalized treatment, they will be asked informed consent for the use of their patient data and for the questionnaires as the control group. As this introduces a bias, the PEID study group will be compared to a historical cohort of Amsterdam MS Center. Furthermore, the patients of the control group will also be asked to donate blood once for measuring of natalizumab trough concentration.

Intervention

Measuring natalizumab concentration and personalizing the interval
Prior to the natalizumab infusion, blood (5cc) will be taken from the drip feed to measure the serum natalizumab trough concentration. Only when sampling through the drip feed is not possible, patients will visit the laboratory for measurement of natalizumab concentration. All blood will be send to Sanquin Laboratory in Amsterdam. Sanquin Laboratory has an excellent logistic system with nearly all hospitals in the Netherlands having a daily or 3-weekly courier. Results of the natalizumab concentration is sent back to the hospital within 2 weeks. Before the start of the new PEID protocol, the natalizumab trough concentration will be tested. All patients that are currently on a 4

week or 5 week interval will then switch to a 6 week interval. The natalizumab trough concentration will be measured every 3 consecutive treatments on the 6 week interval. For patients in the PEID study group with a current treatment interval of >= 6 weeks, the personalized schedule will be based on the natalizumab trough concentration.

Baseline assessment
A digital online national database will be used for entering the patient data. Baseline information includes: age, date of diagnosis, start of natalizumab treatment, JC virus state and index and baseline natalizumab trough concentration measurements. Furthermore, patients will receive a digital questionnaire regarding disease burden and MS related symptoms (Multiple Sclerosis Impact Scale; MSIS-29)24, a questionnaire regarding impact, convenience, satisfaction and side-effects of treatment (Treatment Satisfaction Questionnaire for Medication; TSQM), a questionnaire regarding the wearing-off effect and questionnaires for cost-utility analysis: treatment inventory of costs in patients (TIC-P), EuroQol 5D (EQ-5D) and the Work Productivity and Activity Impairment Questionnaire; Specific Health Problem (WPAI-SHP). A re-baseline MRI-brain scan without gadolinium will be performed before start of the new protocol when the previous MRI scan was >3 months ago and no MRI scan is planned in the upcoming months. The advised MRI protocol consists of a 3D fluid-attenuated inversion recovery and axial PD/T2-weighted sequences.

Yearly routine assessment
After the start of the personalized treatment, natalizumab trough concentrations will be measured after every 3 infusions. Following routine follow-up in natalizumab treated patients with RRMS, patients receive a yearly clinical and radiological (MRI-brain) assessment. The advised MRI protocol consists of a 3D fluid-attenuated inversion recovery and axial PD/T2-weighted sequences. Furthermore, current protocol states a 6 monthly assessment of the JC virus. In the study database, we will collect data regarding the treatment schedule, follow-up natalizumab concentration, yearly MRI, (estimated) Expanded Disability Status Scale (EDSS), relapses during the last year and the JC virus state and index. Patients will receive the digital questionnaires after approximately the first and second year. regarding the quality of life after the first year of PEID. Follow-up will last 2 years. After the trial, patients can, in agreement with their treating neurologist, decide to stay on their personalized natalizumab treatment interval.

For patients switching from IV to SC administration of natalizumab, the trough natalizumab concentration will be measured before every infusion for two years starting from the first SC dose.

Study burden and risks

There is a minimal chance of increase of disease activity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Diagnosis of relapsing remitting multiple sclerosis according to the 2017 criteria
• 6 or more consecutive natalizumab infusions
• 18 years or older

Exclusion criteria

• High titer natalizumab (>100AU/ml) antibodies
• Contraindication for frequent magnetic resonance imaging (MRI)

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-02-2020
Enrollment:	481
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tyruko
Generic name:	Natalizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tysabri
Generic name:	Natalizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	29-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	19-12-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	28-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-513105-31-00
EudraCT	EUCTR2019-002566-13-NL
ClinicalTrials.gov	NCT04225312
CCMO	NL70503.029.19