A prospective, methodology study to identify potential biomarkers of myelin dynamics in CSF using metabolic labeling with stable isotopes in healthy volunteers

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Primary Objective• To demonstrate feasibility of measuring deuterium incorporation into galactosylceramides within the quantitation limits of the assay, in human CSF after chronic dosing of D2O.• To develop a mathematical model to allow estimation...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Demyelinating disorders
Study type	Observational invasive

Summary

ID

NL-OMON38481

Source
ToetsingOnline

Brief title
Biomarkers of myelin dynamics in CSF

Condition

- Demyelinating disorders

Synonym
Multiple sclerosis, nerve disease

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Biogen Idec

Intervention

Keyword: Biomarker, CSF, Deuterium, Myelin

Outcome measures

Primary outcome

Fractional synthesis rate of galactosylceramide (fGalC)

Secondary outcome

• Fractional synthesis rate of sulfatide (fSulft).

• Percentage D2O enrichment in body water as determined in urine and plasma.

• (Myelin) lipid and proteins markers in plasma samples.

• Total concentration of galactosylceramide and sulfatide in the CSF.

Safety/tolerability endpoints:

• AEs leading to premature discontinuation of D2O.

• Treatment-emergent (S)AEs up to 5 half-lives after D2O discontinuation.

• Change from baseline to end-of-study in vital signs: blood pressure and heart rate.

• Treatment-emergent ECG abnormalities up to 5 half-lives after D2O discontinuation.

• Treatment-emergent marked laboratory abnormalities up to 5 pharmacokinetic half-lives after D2O discontinuation

Study description

Background summary

Multiple sclerosis (MS) is the most important inflammatory disease of the central nervous system in the Western world.
This inflammatory disease is characterized by demyelination that results from breakdown of myelin with a subsequent relative failure of the spontaneous remyelination process. Current treatment of multiple sclerosis is aimed at inhibition of the inflammatory component causing the demyelination. Enhancement of remyelination may improve recovery after an exacerbation.
The myelin sheath that surrounds most axons in the brain is a spiral structure that consists of extensions of the plasma membrane of oligodendrocytes. In the adult brain, the components of myelin have different turnover rates. Several dynamic changes due to the degradation and synthesis of the lipid and protein components of myelin occur during demyelination and remyelination, respectively. The ability to monitor the processes of demyelination and remyelination will be necessary to be able to quantify the response therapeutic interventions targeting remyelination, but may also be valuable to track disease activity in demyelinating disorders.
This study aims to develop a metabolic labeling methodoly using non-radioactive, stable isotope labeling combined with mass spectrometric analyses to measure the turnover kinetics of the myelin specific lipids, galactosylceramides (GalC), and sulfatides in human CSF. For this purpose, healthy human subjects are administered with D2O (deuterated water, 2H2O or *heavy water*), wherein the stable isotope deuterium (2H) is incorporated into biomolecules including lipids that were newly synthesized during the duration of label exposure. After degradation, these molecules will be measured in CSF that will be obtained through lumbar punctures.

Study objective

Primary Objective
• To demonstrate feasibility of measuring deuterium incorporation into galactosylceramides within the quantitation limits of the assay, in human CSF after chronic dosing of D2O.
• To develop a mathematical model to allow estimation of the kinetics of myelin turnover based on myelin breakdown products in CSF after chronic labeling with deuterium.

Secondary Objectives
• To determine the fractional synthesis rate of sulfatide (fSulft).
• To determine the D2O enrichment in body water using urine.
• To measure total concentration of galactosylceramide and sulfatide in the CSF.
• To determine the intra-individual variability of galactosylceramide and

sulfatide in CSF of healthy subjects.
• Evaluate the safety and tolerability of drinking D2O for a longer period of time.

Exploratory Objectives
• Evaluate dynamic proteomics of other proteins and lipids in the CSF and plasma samples.
• Determine galactosylceramides in urine.

Study design

Study in 6 healthy volunteers to investigate if D2O administration results in deuterium labeling of myelin. Quantification of absorption will be determined in CSF, plasma and urine.
• 6 subjects that meet the recruitment criteria will be instructed to consume two doses of 60 mL 70% D2O every day for ten weeks. Urine samples will be collected once a week to measure the percentage D2O in body water.
• the subjects will receive 4 lumbar punctures (LP) for CSF and concurrent venous punctures for plasma collection. These are scheduled 35, 70, 94 and 167 days after start of the study.

Study burden and risks

Possible burdens:
- Bruising at the place of venapunction
- The possible side-effects from the lumbar puncture (for example headache, low bloodpressure, nausea and dizziness).
- Findings during tests (i.e. positive test result for hepatitis B, hepatitis C or HIV).
- Drinking heavy water can cause dizziness. However, because the amounts are small, we don't expect this side-effect (based on literature).

The healthy volunteers will not benefit from this study. The methodology can be used in future studies to prove the effectiveness of pharmaceutical compunds improving remyelinization, benefiting MS patients.

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

- Signed informed consent prior to any study-mandated procedure;
- Males or females, aged 18-70 years;
- BMI between: 18-30 kg/m2, minimal weight 50 kg
- Ability to communicate well with the investigator in the Dutch language.
- Ability to easily visit CHDR in Leiden oncea week
- Expected compliance to the protocol with respect to drinking D2O 2 times every day for 70 days

Exclusion criteria

- Clinically significant abnormalities, as judged by the Investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In case of uncertain or questionable results, tests performed during screening may be repeated before the first occasion to confirm eligibility or judged to be clinically irrelevant.
- Subject is pregnant or breastfeeding.
- Any contraindication for a lumbar puncture.
- Recent (within 60 days) or current use of medications.
- Participation in a clinical trial within 90 days of screening or more than 4 times in the previous year.
- Positive test for drugs of abuse at screening or pre-dose.

- Alcohol is prohibited from 24 hours before screening and the first visit.
- History or symptoms of any significant disease including (but not limited to) neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder.
- Positive hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
- Donation of blood over 500 mL within 3 months prior to screening.
- Unwillingness or inability to comply with the study protocol for any other reason.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-06-2013
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO

Date:	21-06-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	11-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
CCMO	NL45011.056.13