Imaging activated microglia in relapsing remitting multiple sclerosis: a first in human P2X7r PET study

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To assess activated microglia in vivo in clinically and/or radiologically active RRMS patients compared to healthy controls using the PET-tracer [11C]SMW139, to assess retest variability in regional [11C]SMW139 brain uptake, and to evaluate which...

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

Summary

ID

NL-OMON47369

Source
ToetsingOnline

Brief title
M1MS

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: Ministerie van OC&W,Merck,Merck Serono;zie G2

Intervention

Keyword: Microglia, Multiple Sclerosis, P2X7 receptor, Positron Emission Tomography (PET)

Outcome measures

Primary outcome

- To determine whether binding of the P2X7-receptor radioligand [11C]SMW139 in the brain in vivo can discriminate active RRMS patients from healthy controls.

- To assess retest variability in regional [11C]SMW139 brain uptake

- To evaluate which tracer kinetic method is the most suitable for quantification of [11C]SMW139 binding.

Secondary outcome

- To determine whether [11C]SMW139 binding is increased in T2 hyperintense lesions and T1 gadolinium enhancing on MRI.

- To determine whether [11C]SMW139 binding correlates with clinical disability in clinically and/or radiologically active RRMS patients.

Study description

Background summary

The pathophysiology of MS is currently unclear. Microglia activation can be used as an indirect marker to assess neuroinflammation in MS. For the past twenty years this has been studied in MS patients with the use of TSPO PET-tracers. However, TSPO as microglial imaging target has several limitations, e.g. intracellular localization, various polymerization states, genetic binding differences. Therefore, new microglial targets, including the purinergic receptor family, have been investigated as alternative membrane-based receptors to serve for in vivo assessment of microglial activation.

Study objective

To assess activated microglia in vivo in clinically and/or radiologically

active RRMS patients compared to healthy controls using the PET-tracer [11C]SMW139, to assess retest variability in regional [11C]SMW139 brain uptake, and to evaluate which tracer kinetic method is the most suitable for quantification of [11C]SMW139 binding.11C]SMW139 binding.

Study design

We will include 10 RRMSpatients and 10 healthy controls. For both the MS patients and healthy controls this study will consist of three parts:
1. First study visit at the Neurology outpatient clinic for a neurological and physical examination, questionnaires and venous blood sampling
2. MRI scan, for the patient group with administration of the contrast agent gadolinium.
3. Two [11C]SMW139 PET-CT scans with arterial blood sampling on the same day (test-retest)

Study burden and risks

Risks associated with participation in this study are related tot 1) radiation exposure, 2) idiosyncratic reaction to the tracer, 3) placement of in intra-venous and intra-arterial catheter, 4) discomfort during the scanning, 5) blood sampling, 6) coincidental finding.
1) The two [11C]SMW139 PET-CT scans will result in a total radiation burden of 6 mSv. This falls in de International Commission on Radiological Protection (ICRP) risk category IIb. Radiation exposure in this category is justified if it is directly aimed at the cure or prevention of disease, as is the case for this protocol.
2) Based on the extensive experience with PET-tracers in our center, idiosyncratic reaction to the venously administered tracer [11C]SMW139 is not rendered likely. During each injection of the tracer a physician will be present.
3) Intravenous and intra-arterial cannulation is associated with a very small risk of infection and bleeding. This will be prevented by the use of proper techniques by experiences personel.
4) It may be uncomfortable to lie motionless in the MRI and PET scanners and it may cause some subjects to fell anxious. Subjects will be made acquinted with the surroundings beforehand. Moreover, our staff will be available to provide support, reduce anxiety, optimise the comfort of subjects and if requested remove subjects from the scanner.
5) Adverse effects of blood sampling will be minimised by exclusion of subjects with low haemogolibin levels (in males Hb < 8.0 mmol/litre, in females Hb < 7.0 mmol/litre). No more than 500 ml blood will be withdrawn during the total PET procedure and screening.
6) With the blood tests and MRI-scan a coincidental finding may occur. If such a new finding has consequences for the subject, the subject and his/her general practitioner will be informed. If a patient or healthy control does not want to

be informed on such a coincidental finding, this subject can not partake in this trial.

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

- For the MS patient group: diagnosis of relapsing remitting MS with clinically or radiologically active disease
- 20 to 60 years old
- Written informed consent

Exclusion criteria

- Current or recent immunomodulating or immunosuppressive therapy, excluding first-line MS treatment started less than 3 months prior to the PET-scans.
- Inability to undergo MRI and PET scan (metal objects in or around the body, claustrophobia or inability to lie still in the scanner) and for the patient group contra-indication for gadolinium administration
- Significant immune disease other than MS
- (History of) other relevant neurological disease
- Known allergy including, but not limited to, hay fever, dust mite allergy and allergies to cats or dogs
- Known asthma
- History of malignancy
- Known significant cardiac disease
- Inadequate renal function: creatinine clearance <60 ml/min
- In male subjects Hb <8.0 g/dL, in female subjects Hb <7.0 g/dL
- Pregnant or breast feeding
- (History of) alcohol and/or drug abuse
- Exposure to previous radiation leading to annual cumulative dose of more than 10 mSV if participating in this protocol

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[11C]SMW139
Generic name:	NvT

Ethics review

Approved WMO Date:	07-12-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2018
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
EudraCT	EUCTR2016-003617-98-NL
CCMO	NL59118.029.16