[11C]MeDAS PET: a non-invasive imaging tool for quantitative assessment of myelin loss in multiple sclerosis

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

Summary

ID

NL-OMON46348

Source
ToetsingOnline

Brief title
Myelin PET in MS

Condition

- Demyelinating disorders

Synonym
MS, multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: MS, myelin, PET

Outcome measures

Primary outcome

The main study endpoint is demyelinated lesion detection using [11C]MeDAS PET imaging with an optimal data analysis method for quantification of myelin binding.

Secondary outcome

Secondary study endpoints are:

* A decreased patient burden by implementation of simplified analysis methods for quantitative [11C]MeDAS PET imaging of myelin without using arterial blood sampling.

* Test-retest variability of the simplified analysis methods

* The correlation between PET and MRI findings

Study description

Background summary

Multiple sclerosis (MS) is a disease, in which myelin sheaths in the brain and spinal cord are damaged. If repair of myelin damage is incomplete, nerve terminals will be irreversibly destroyed, leading to neurological symptoms. Ineffective remyelination is probably a major underlying mechanism resulting in irreversible neurological impairments in the progressive phase of MS. Most therapies aim to stop inflammatory processes associated with the myelin damage, but all lack efficacy in progressive MS so far. Strategies that promote myelin repair are promising, but still under investigation. Non-invasive imaging of myelin damage and repair could enable better disease characterization and accelerate evaluation of new interventions. Although MRI is successfully used in MS diagnosis, it cannot quantify myelin changes. We have recently demonstrated in animal models for MS that damage and repair of myelin can be

visualized and quantitatively measured by PET using the newly developed tracer [11C]MeDAS. We now aim to make [11C]MeDAS PET available for clinical investigations of myelin density in the brain and spinal cord. The scanning procedure will be validated in patients with progressive MS and correlated to MRI results and (changes in) clinical symptoms.

Study objective

We and others have clearly demonstrated in animal models of MS that the [11C]MeDAS PET signal correlates well with myelin density and therefore can be used to monitor myelin loss and repair in vivo. These promising preclinical results warrant translation to application in humans. The objective of this project is to evaluate [11C]MeDAS PET as a quantitative method for assessment of myelin density and to develop the optimal scanning protocol for application in humans.

Study design

This study will evaluate [11C]MeDAS PET in patients with Multiple Sclerosis and assess the analysis methods to obtain reliable quantitative PET measures. Based on clinical history and available MRI scans, 5 SPMS patients and 5 PPMS patients will be included. All will receive a [11C]MeDAS PET scan at baseline and another [11C]MeDAS PET scan one week later, in order to investigate the test-retest variability in the measures of myelin density. Information on test-retest variability is especially important when longitudinal changes or response to therapy is measured. For the first PET scan, a venous catheter and a wrist arterial cannula will be placed. Approximately 400 MBq of [11C]MeDAS will be injected during 1 minute intravenously (IV) followed by a flush. Immediately following injection, a dynamic 70 minute PET scan will be performed. Arterial blood will be withdrawn continuously from 0-60 minutes using an online detection system which will be cross-calibrated against the PET scanner. At set times, additional manual blood samples will be taken to measure whole blood and plasma radioactivity concentrations. In addition, plasma samples will be used to determine the fraction of radioactivity that corresponds to intact [11C]MeDAS. No more than 175cc of blood will be withdrawn during the PET session. After the first PET scan, a MRI scan is performed. The sequences used are T1 with gadolinium contrast, T2 and FLAIR, which are standard sequences for multiple sclerosis, furthermore myelin MRI and perfusion MRI is performed using the same gadolinium contrast (0.2 mmol/kg Dotarem) as for the acquisition of the T1 sequence. The perfusion MRI scan is performed to discriminate whether differences in PET tracer uptake are caused by microvascular damage (decreased tracer delivery) or a decrease in myelin density. Approximately one week following the baseline scan, subjects will return to the clinic for a second [11C]MeDAS PET scan. Subjects will undergo the same safety procedures as the baseline PET visit except for arterial catheter placement, arterial blood sampling and MRI scan. If there are any

hitherto unknown clinically relevant abnormalities these will be communicated to the subjects* general practitioner in line with METc/IRB guidelines.
Following each [11C]MeDAS PET visit, a follow-up phone call to the subject will be conducted 2 or 3 business days after the imaging day, but not before 48 hours post-injection, to confirm the subject*s well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

Intervention

There will be two [11C]MeDAS PET scans performed to assess the feasibility and test-retest variability of this myelin imaging method. The first [11C]MeDAS PET scan will be performed with arterial blood sampling and the second [11C]MeDAS PET scan will be done without. In addition, a MRI scan will be performed for co-registration of the PET images and for obtaining anatomical information to determine regional tracer uptake.

Study burden and risks

At present, there is no adequate method to quantify myelin loss and restoration in lesions of MS patients. Absence of such a method hampers the development of treatments that aim to restore myelin damage in MS patients. [11C]MeDAS PET will be validated as a imaging method to quantitatively assess myelin density in MS patients. Clinical validation of [11C]MeDAS PET is an important step to move research on innovative treatments that stimulate myelination in MS lesions forward. Moreover, the method could enable better patient characterization, stratification and evaluation of treatment strategies.
[11C]MeDAS is a myelin radioligand which provide most promising results as a myelin tracer in animal studies. However, no clinical data are available for this tracer yet. The LD50 of [11C]MeDAS in mice was determined to be 141 mg/kg. For a PET scan in humans, a typical dose of 400 MBq [11C]MeDAS is injected, which corresponds to a mass of less than 4 µg of the tracer. This microdose of the PET tracer is 6 orders of magnitude lower than the LD50 in mice. Therefore no toxicological effects are expected for a tracer dose of [11C]MeDAS.
In mice, highest tracer uptake was observed in liver, lung, brain, GI tract and adrenals. After administration of [11C]MeDAS in mice, almost all activity in the organs consisted of the intact tracer. The radioactive metabolites of [11C]MeDAS in plasma, were all more hydrophilic than the intact tracer, suggesting that metabolites are less likely to cross the blood-brain barrier.
No adverse effects were observed when a tracer dose of [11C]MeDAS was injected in mice or rats.
The estimated effective dose in humans based on the finding in mice is 2.99µSv/MBq, which is comparable to other 11C-labeled PET tracers. For an injected dose of 400 MBq [11C]MeDAS, the effective dose corresponds to a radiation burden to the patient of 1.2 mSv, 1.8 mSV per scan and 3.6 mSv for the complete study,

which is within category IIb (1-10 mSv; minor to moderate risk), as defined by the International Commission on Radiological Protection (ICRP).

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

* At least 18 years of age
* A diagnosis of primary or secondary progressive MS
* Sign an Institutional Review Board (IRB) approved informed consent form prior to any study procedures
* Subjects who, in the opinion of the principal investigator, can tolerate the [11C]MeDAS PET, MRI and blood sampling procedures

Exclusion criteria

* Women who are pregnant or breast feeding
* Clinical history of diminished renal and/or liver function
* Inability to undergo MRI-scanning due to presence of materials in the body that can be magnetized and cannot be removed
* Claustrophobia
* Current clinically significant cerebrovascular disease
* Blood donation within 6 months prior to the [11C]MeDAS PET scan
* Current use of any investigational medications, or having participated in a trial with investigational medication within the last 30 days
* In the opinion of the investigator, otherwise unsuitable for a study of this type

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-01-2019
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	08-11-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	07-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2017-005199-24-NL
CCMO	NL64579.042.18