Grey matter microglial imaging with [18F]DPA-714 in progressive MS patients

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

Summary

ID

NL-OMON41799

Source
ToetsingOnline

Brief title
[18F]DPA-714 PET in 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: Ministerie van OC&W

Intervention

Keyword: [18F]DPA-714, Microglia, Multiple Sclerosis, Positron Emission Tomography (PET)

Outcome measures

Primary outcome

The aim of this pilot study is to determine whether uptake can be quantified in the cortex and/or hippocampus in vivo to discriminate progressive MS patients from controls

Secondary outcome

Secondarily we will determine whether:

1. labeled microglial cells co-localize with MRI detected GML and cortical thinning

2. binding in cortex and/or hippocampus correlates with clinical disability and cognitive decline in progressive MS patients

The main objective of this pilot study is to quantify microglia activation in the cerebral grey matter with [18F]DPA-714 PET. As this pilot study has a limit studypopulation, statistically relevant answers to especially the last objective are not expected. This could be analysed in more detail in a possible larger follow up study to this pilot study.

Study description

Background summary

Multiple sclerosis (MS) is the most common nontraumatic cause of neurologic disability in young adults. It is an auto-immune disorder characterized by

inflammatory demyelination and axonal transection in multiple sites throughout the central nervous system. Approximately 80% of patients are initially diagnosed with relapsing-remitting MS (RRMS), in which patients experience relapses of neurological symptoms, followed by a complete or partial remission. With disease progression around 70% of RRMS patients enter a secondary progressive phase, characterized by a steady progression of neurological symptoms. This phase is termed secondary progressive MS (SPMS). In the remaining 20% of patients the disease has a progressive course from disease onset called primary progressive MS (PPMS).

MS has been traditionally regarded as a white matter disorder; however focal demyelination in the white matter as shown on MRI cannot fully explain the neurological and cognitive deficits in MS patients. Histological studies have shown the involvement of grey matter regions in the demyelinating process in predominantly PPMS and SPMS. The importance of this was illustrated by the fact that the extent and severity of cortical/subcortical damage significantly influence the cognitive functions in MS patients. Histological studies have shown that grey matter lesions (GML) formation differs from white matter lesion (WML) formation by a relative absence of infiltrating leukocytes. In line with this, there is limited blood-brain barrier (BBB) damage in progressive MS. A recent post-mortem study showed an abundance of microglial reactivity in these cortical lesions. Combined with the known lack of clinical response of immune-modulating treatment as used in RRMS in patients with progressive disease1, these data indicate that the pathogenesis of neurodegeneration may be different between RRMS and progressive MS phases.

Study objective

The main objective of this study is to depict microglial activation behind a closed BBB in vivo and possibly establish an imaging marker of fast clinical progression, we will aim at visualizing microglial activity in vivo in cortical and hippocampal grey matter of progressive MS patients, and determine its relation to cognition and disability.

Study design

To quantify activated microglia in vivo we will use the tracer [18F]DPA-714. This is a second generation TSPO radioligan of which previous studies have shown a high affinity and specificity for activated microglia. Besides, the binding to 18F makes this tracer als favourable over other 11C bound TSPO radioligand as 18F tracers have a significantly longer half life (109.8 minutes compared to 20.4 minuten). This will increased its clinical use.
For this pilot study we will include 13 PPMS or SPMS patients and 10 healthy controls.

For both the MS patients and healthy contols this study will consist of three

parts:
1. A screenings session with neurological and physical test, questionaires and venous blood sampling.
2. MRI scan qith administration of hte contrast agent gadolinium.
3. PET-CT scan with the use of [18F]DPA-714 and with arterial blood sampling.

Intervention

Intravenous injection of the PET tracer [18F]DPA-714.

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) Administration of 250 MBq of [18F]DPA-714 will result in a radiation dose of approximately 5.25 mSv. The low-dose CT-scan of the brain gives a radiation dose of 0.5 mSv, resulting in a total radiation exposure of 5.75 mSv per subject. 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. This is the case as the role activated microlgia probably play in neuroinflammation and neurodegeneration associated with MS could lead to the development of specific treatment protocols aimed at this neuroinflammatory process.
2) Isiosyncratic reaction to the venously administered tracer [18F]DPA-714 is not rendered likely. [18F]DPA-714 has been used in humans in previous studies and no negative effects have been reported with the use of dosis as described in these studies. 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 250 ml blood will be withdrawn during the total PET procedure and screening. Subjects will be excluded if the have donated blood or lost a significant amount of blood in the four months prior to de PET scan. Besdies, subjects are advised not to donate blood within three months after the PET scan.

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 primary or secondary progressive MS with EDSS scores 4.0 to 7.5
- 18 to 60 years
- Written informed consent

- No immunomodulating or immunosuppressive treatment in previous three months

Exclusion criteria

- Inability to undergo MRI, e.g. metal objects in or around the body, claustrophobia or inability to lie still in the scanner. For the MS patients: contra-indication for gadolinium administration, e.g. previous allergic reaction to gadolinium.
- Homozygote Ala(147)Thr genotype (low-affinity binders)
- Significant immune disease other than MS
- (History of) other relevant neurological disease
- History of malignancy
- Known significant cardiac disease
- Inadequate renal function: creatinine clearance <60 ml/min
- Loss or donation of blood over 500 mL within four months prior to screening.
- 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
- Use of benzodiazepines within 1 week of the PET scan

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-01-2015
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[18F]DPA-714
Generic name:	NvT

Ethics review

Approved WMO Date:	01-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2015
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	EUCTR2014-002547-17-NL

Register	ID
CCMO	NL49636.029.14