Local delivery of CER-001 in advanced plaques
Proof-of-concept for apoA-1 as initiator of reverse cholesterol transport (LOCATION)

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Primary1. To demonstrate that 89Zr-CER-001 penetrates into atherosclerotic plaques in patients by means of PET imaging. Secondary 2. To evaluate whether the amount of 89Zr-CER-001 penetrating the plaque corresponds to athero-lesion severity.3. To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Observational invasive

Summary

ID

NL-OMON40758

Source
ToetsingOnline

Brief title
LOCATION

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerosis, vascular disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Atherosclerosis, CER-001, HDL, Imaging

Outcome measures

Primary outcome

89Zr-CER-001 uptake in the plaque over time, reported as Standardized Uptake Value (SUV), by means of PET imaging.

Secondary outcome

Further quantification of CER-001 uptake at the plaque

- 89Zr-CER-001 uptake in the plaque over time assessed as the Target to Background Ratio (TBR), via PET imaging

- Difference between SUV and TBR at the level of the plaque and SUV and TBR of non-diseased arterial wall on PET

Relation between CER-001 uptake and plaque characteristics

- Relation between SUV and TBR of the plaque on PET and structural plaque dimensions on MRI i.e. normalized wall index, vessel wall area. - Relation between SUV and TBR of the plaque and plaque permeability on DCE-MRI, i.e. Ktrans

Relationship between the CER-001 uptake in the plaque by means of PET imaging reported as SUV of the plaque and the cholesterol efflux capacity.

Study description

Background summary

Atherosclerosis is considered a chronic inflammatory disease in which macrophages play a major role by taking up (oxidized) low-density lipoprotein (LDL). The lipid-laden macrophages accumulate and undergo apoptosis leading to the formation of a necrotic core and eventually the vulnerable plaque.

Cholesterol efflux from lipid-laden macrophages is a key atheroprotective mechanism, a process referred to as reverse cholesterol transport (RCT) in which apolipoprotein (apo)A-1 and HDL particles remove cholesterol from peripheral cells. In view of the abundant evidence for apoA-1 on stimulating efflux from macrophages in vitro, it is reasonable to assume that apoA-1 will also stimulate efflux from vessel wall macrophages in vivo if apoA-1 succeeds in getting into the proximity of plaque macrophages.

The radio-isotope Zirconium-89 (89Zr) has emerged as a *gold-standard* in the field of antibody-based PET imaging. The experience in oncology and the fact that 89Zr-labeling is a GMP-approved method makes this a suitable candidate for proving target delivery of apoA-1/HDL into advanced atherosclerotic plaques in humans using non-invasive imaging techniques. With this project we aim to show that exogenously infused apoA-1 (CER-001®) penetrates into advanced plaques in patients, making it *highly likely* that efflux of cholesterol from macrophages to the apoA-1/HDL complex will occur.

Study objective

Primary
1. To demonstrate that 89Zr-CER-001 penetrates into atherosclerotic plaques in patients by means of PET imaging.

Secondary
2. To evaluate whether the amount of 89Zr-CER-001 penetrating the plaque corresponds to athero-lesion severity.
3. To evaluate whether the amount of 89Zr-CER-001 penetrating the plaque corresponds to plaque permeability.
4. To evaluate whether the amount of 89Zr-CER-001 penetrating the plaque corresponds to the cholesterol efflux capacity

Study design

This study is designed as a single-center, observational study. Patients with a very high cardiovascular risk and signs of atherosclerotic lesions in the ascending aorta or carotid arteries (evaluated using ultrasound and/or MRI)

will be subjected to a (DCE-) MRI. Subsequently, 89Zr labelled CER-001 (3mg/kg) is infused (18Mbq) where after low-dose PET/CT of the aorta and carotid arteries is performed. Starting with a PET/CT-scan 10 minutes after infusion followed by a scan at 24 and 72 hours after.

Study burden and risks

The results of this study will add to our understanding on the role of CER-001 as an anti-atherosclerotic strategy: if CER-001 accesses the atherosclerotic lesion, it is highly likely that CER-001 is able to induce efflux from cholesterol-laden macrophages within atherosclerotic lesions. Patients receive no direct benefits, however these research results will increase the likelihood of CER-001 to enter a clinical development program targetting regression of severe atherosclerosis in patients with similar critera as those inncluded in the present study. The maximum radiation exposure of the infusion of 89Zr -labeled CER-001 and 3 sequential low-dose CT scans is 18 mSv

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

Patients must meet the following criteria for study entry:
- Adult patients (either gender) * 50 years
- Documented atherosclerotic vascular disease; defined as carotid artery stenosis > 50% on clinical MRI or ultrasound.
- Clinically stable for at least 3 months prior to inclusion

Exclusion criteria

Patients are not eligible if they meet one of the criteria listed below:
- Creatinine clearance < 50 ml/min (MDRD) 6 months prior to inclusion
- Auto-immune disease/vasculitis, other active inflammatory diseases, proven or suspected bacterial infections. Recent (< 1 month prior to inclusion) or ongoing serious infection requiring IV antibiotic therapy that could interfere with the conduct of the study in the opinion of the investigator
- Known systemic disorders such as hepatic, renal, hematologic, and malignant diseases or any clinically significant medical condition that could interfere with the conduct of the study in the opinion of the investigator
- Standard contra-indications to MRI, PET, and CT
- Inability or unwillingness to comply with the protocol requirements, or deemed by investigator to be unfit for the study

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-07-2014
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-CER-001
Generic name:	89Zr-CER-001

Ethics review

Approved WMO Date:	23-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2014
Application type:	First submission
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

ID: 22856
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2014-001666-10-NL
CCMO	NL49081.018.14
OMON	NL-OMON22856