A Proof of Concept Study to Determine the Local Delivery and Efficacy of Intravenously Injected PEG-Liposomal Prednisolone Sodium Phosphate (Nanocort®) in Atherosclerotic Tissue in Subjects with Peripheral Artery Disease.

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1. To proof local delivery of intravenously administered liposomal glucocorticoids (Nanocort) in subjects with peripheral artery disease by demonstrating Nanocort in atherosclerotic tissue. 2. To determine the differences between cytokine production...

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

Summary

ID

NL-OMON37733

Source
ToetsingOnline

Brief title
DELIVER

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerosis, peripheral artery 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: Glucocorticoids, Local delivery, Vessel wall inflammation

Outcome measures

Primary outcome

Quantity of PEG liposomes in the atherosclerotic plaque and/ or in

atherosclerotic macrophages as determined with a PEG antibody quantitative

sandwich ELISA.

Secondary outcome

Differences in concentration of corticosteroids in the atherosclerotic plaque

and/or in atherosclerotic macrophages.

Differences between TNF-alpha levels in the supernatant of isolated macrophages

from the atherosclerotic tissue as determined by quantitative sandwich ELISA

Study description

Background summary

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in developed nations. CVD is primarily caused by atherosclerosis, a systemic disease characterized by lipid deposition in the subendothelial space with a concomitant, low-grade inflammatory reaction.
A promising strategy to reduce CVD is to directly target inflammation at the level of the vessel wall. A potential drawback of anti-inflammatory strategies pertains to the thin line between inhibiting *inappropriate* inflammation

versus inducing immuno-suppression. One of the strategies to limit systemic immunosuppression is to strive for local delivery of the drug by encapsulating the compound in liposomes.
Liposome-encapsulated drugs efficiently target lesions and accumulate at a much higher extent at desired areas of interest. This approach is currently used for the clinical treatment of different types of cancer (liposomal doxorubicin) and fungal infections (liposomal amphotericine-B). Liposomes for other applications (rheumatoid arthritis, cystic fibrosis, multiple sclerosis and atherosclerosis) are being pre-clinically developed or investigated in clinical trials.
Recent pre-clinical studies in animal models corroborate that liposomal glucocorticoids effectively attenuate atherosclerotic plaque inflammation and exhibit improved pharmacokinetics and biodistribution. Also, local delivery through localization of liposomes at inflammatory sites and in local macrophages was demonstrated in animal models.
In humans, the potential of PEG-liposomes to target inflammatory sites has been showed by imaging of radioactive liposomes.
However, the concept of local delivery and efficacy of liposomal corticosteroids at the inflammatory sites, such as atherosclerosis, and at local macrophages remains to be determined in humans. In the present project, we aim to evaluate the delivery and efficacy of intravenously administered liposomal glucocorticoids (Nanocort) compared to systemic infused corticosteroids or placebo in patients with peripheral artery disease.

Study objective

1. To proof local delivery of intravenously administered liposomal glucocorticoids (Nanocort) in subjects with peripheral artery disease by demonstrating Nanocort in atherosclerotic tissue.

2. To determine the differences between cytokine production of isolated atherosclerotic macrophages from patients with peripheral artery disease treated with liposomal glucocorticoids (Nanocort), systemic glucocorticoids (Methylprednisone) or placebo.

Study design

A proof-of-concept, multi-center(AMC en Flevoziekenhuis), randomized, placebo-controlled study evaluating the concept of local delivery of intravenously injected PEG-liposomal prednisolone sodium phosphate (Nanocort) versus Methylprednisolone or placebo in subjects scheduled for operation due to peripheral artery disease.

Intervention

Subjects will be randomized to either Nanocort, Methylprednisolone or placebo (saline) infusion using a 1:1 ratio on day 10±1 and day 3 ±1 before the

operation date.

Study burden and risks

The results of this study contribute to the development of novel anti-inflammatory directed atherosclerotic treatment strategies. Patients receive no direct benefits.

Patients should visit the AMC or Flevoziekenhuis 2 times, besides the day of their scheduled endarterectomy. There are 2 infusions of Nanocort, Methylprednisolone or placebo, patients may experience these infusions as a burden.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
1105AZ
NL

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: ;1) Patients scheduled for endarterectomy due to peripheral artery disease.;2) If using a statin, on stable therapy for at least 6 weeks prior to screening with no evidence of statin intolerance.;3) For patients taking angiotensin-converting enzyme (ACE) inhibitors (ACE-I) or angiotensin-receptor blockers (ARBs), non-statin lipid-modifying therapy, thiazolidinediones, inhaled steroids, or leukotriene modifying agents, use of a stable dose for at least 6 weeks prior to baseline measurement.;4) For patients taking Nonsteroidal anti-inflammatory drugs (NSAIDS), Cyclo-oxygenase-2 inhibitors (COXIBs), use of a stable dose for at least 6 weeks prior to baseline measurement.

Exclusion criteria

Subjects may not enter this study if they meet the following criteria: ;1) Current medical history of Auto-immune disease/vasculitis, active inflammatory diseases, proven or suspected bacterial infections. Recent (<1 month prior to screening) or ongoing serious infection requiring IV antibiotic therapy. ;2) Recent or current treatment with medications that may have a significant effect on plaque inflammation, including but not limited to: ;* Steroids for at least 6 weeks prior to baseline measurement and during study (with the exception of inhaled steroids).;* Biological based medicines (anti-TNF (ex. Infliximab), anti-IL-6 therapy (ex. Tocilizumab) or anti-IL-1 (ex. anakinra)) within 8 weeks before the baseline visit and during the study;* No other Disease modifying antirheumatic drugs (DMRADS) within 6 weeks of baseline and during study (such as cyclosporine, azatioprine, etc.);3) Known systemic disorder, such as hepatic, renal, hematologic or endocrine diseases, infections or malignancies, or any clinically significant medical condition that could interfere with the conduct of the study. ;4) Subjects with a known ulcus ventriculi or duodeni.;5) Female subjects who are breastfeeding, pregnant or trying to get pregnant. ;6) History of anaphylaxis, anaphylactoid (resembling anaphylaxis) reactions, or severe allergic responses.;7) History of hypersensitivity to methylprednisolone or any component of the formulation.;8) Any history of myopathy or a history of neuromuscular disorders (e.s, myasthenia gravis).;9) Any planned vaccinations.;10) Inability or unwillingness to comply with the protocol requirements, or deemed by investigator to be unfit for the study.;11) Subject has planned cardiac surgery, PCI or carotid stenting, or major non-cardiac surgery during the course of the study period or for 14 days after the last treatment. Subjects scheduled for endarterectomy are not excluded.
12) Current medical history of drug or alcohol abuse within 12 months prior to screening.;13) Subjects are not permitted to enter the study if they have taken any investigational drug in the 3 months prior to study drug administration.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-05-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nanocort
Generic name:	Liposomal prednisolone
Product type:	Medicine
Brand name:	Solu-Medrol
Generic name:	Methylprednisolone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-02-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	23-04-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	30-05-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2012
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	EUCTR2012-000543-27-NL
CCMO	NL39717.018.12