Doxycycline for Stabilization of Abdominal Aortic Aneurysms

Published: 26-07-2007
Last updated: 09-05-2024

To test whether 100 mg doxycycline inhibits aneurysm growth

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Aneurysms and artery dissections
Study type	Interventional

Summary

ID

NL-OMON31047

Source
ToetsingOnline

Brief title
Doxy-study

Condition

- Aneurysms and artery dissections

Synonym
abdominal aortic aneurysm

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Abdominal Aneurysm, Doxycycline, Growth, Stabilization

Outcome measures

Primary outcome

Aneurysm progression at t=18 months

Secondary outcome

Seconday outcome measures are growth at 6 and 12 months, need for elective aneurysm repair, rupture, death, and an inventory of possible side-effects (questionnaire). Moreover, possible beneficial effects of doxycycline therapy on the progression of atherosclerosis and emphysema will be evaluated by assessment of intima media thickness (carotid artery), plasma inflammatory markers (CRP, fibrinogen) and endothelial cell markers (sICAM, von Willebrand factor), and spirometric testing (FEV1, FVC, FEV1/FVC, VC).

Study description

Background summary

An abdominal aortic aneurysm (AAA) affects 5-7% of people over 60, and is responsible for more than 15.000 deaths annually in the US alone. For unknown reasons, the incidence has been steadily increasing over the last two decades, and a further increase is anticipated. Current approaches towards AAA are surveillance, and preventive surgical elimination ('repair') of AAA over 5.5 cm. Unfortunately, traditional (open) elective AAA repair is associated with a relatively high morbidity and mortality. Although short-term results of endovascular repair appear more favourable, mid- and long-term mortality is similar to that of conventional repair. Moreover, the high incidence of endograft failure repair requires life-long follow-up. According to the available studies, including a Dutch randomized trial, endovascular repair is currently not cost-effective. Hence availability of medical therapy, inhibiting aneurysmal growth and reducing the need for invasive treatment, could have major advances both from patients' as well as from socio-economical perspective. Increased activities of the matrix metalloproteinases, in particular MMP-9, are considered a key-factor in AAA development and growth. The tetracycline analogue doxycycline attenuates both MMP expression and activity. It was thus hypothesised that doxycycline may prevent AAA growth. Indeed, doxycycline has

been shown to prevent aneurysm formation in animal models of the disease. Results from two small clinical studies suggest that doxycycline treatment may also arrest AAA growth in patients with medium sized aneurysm.
We evaluated the effect of pre-operative doxycycline treatment in patients undergoing conventional AAA repair (NHS 2000B165), and confirmed the effects of doxycycline on expression of the gelatinase MMP-9. Our results also revealed remarkable suppression of MMP-8 (neutrophil collagenase) protein expression. These findings are new and remarkable. MMP-8 is a stored secondary granule protein that is only expressed during the late myeloid maturation pathway of neutrophils, but not in mature, infiltrating neutrophils. This suggests that the effect of doxycycline on aneurysm growth may extend beyond the effect on MMP expression and involves attenuation of neutrophil influx. We confirmed the effect on neutrophil influx by immunohistochemical analysis and explored the mechanism underlying reduced neutrophil influx. This analysis showed that that doxycycline, via its effects on the transcription factors AP-1 and C/EBP, profoundly reduces IL-6 and IL-8 hyperexpression in AAA. This not only results in reduced neutrophil influx, but also in attenuation of cytotoxic T-cell activation.
Doxycycline has a well-established safety record, is generally well tolerated and is inexpensive. Doxycycline should thus be considered a promising lead-candidate for the pharmaceutical stabilization of AAA.

Study objective

To test whether 100 mg doxycycline inhibits aneurysm growth

Study design

a prospective, randomized placebo controlled trial of standard dose doxycycline or placebo

Intervention

doxycyline 100 mg

Study burden and risks

Minimal, doxycyline is an established drug with an excellent safety profile

Contacts

Public
Leids Universitair Medisch Centrum

Postbus 9600
2300RC Leiden
NL
Scientific
Leids Universitair Medisch Centrum

Postbus 9600
2300RC Leiden
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Patients with an abdominal aortic aneurysm
• The diameter should be 3.5 - 5.0 cm (Group A)
• The diameter is > 5.5 cm and the patient is unfit for operation or refuses intervention (Group B)
• Follow-up with ultrasound should be possible (obesity)

Exclusion criteria

• Unable to comply with follow-up
• Contra indications for doxycycline (excessive sun exposure)
• Known impaired liver function (ALAT >3-fold normal values) or known kidney dysfunction (estimate clearance less than 40 ml/min)
• Excessive sun exposure

Study design

Design

Study phase:	3
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):	10-11-2008
Enrollment:	300
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Doxycycline
Generic name:	Doxycycline
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	26-07-2007
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2007-004124-20-NL
CCMO	NL18925.058.07