Pharmaceutical Aneurysm Stabilisation Trial

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AAA is a common disease and a major cause of death due to rupture. Preventive surgical aneurysm repair is costly and associated with considerable morbidity and mortality. Doxycycline has been shown to attenuate the expansion of aneurysm in animal...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON23083

Bron
NTR

Verkorte titel
PHAST

Aandoening

Abdominal aortic aneurysm - Inflammation - Cardiovascular diseases - Metalloproteinases - Doxycycline - Pharmaceutical Treatment

Ondersteuning

Primaire sponsor: Nuts Ohra
Overige ondersteuning: LUMC

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

* Aneurysm growth at t=18 months as determined by ultrasound

Toelichting onderzoek

Achtergrond van het onderzoek

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. Yet, its
efficiency remains to be established in a prospective, sufficiently powered clinical trial. We therefore propose to
evaluate the effects of doxycycline (standard dose, 100 mg/day) on AAA growth in a double blind placebo
controlled multi-centre study in patients under surveillance for a small (3,5-5,0 cm) or patients with larger (over 5,5
cm) AAA who are unfit for or refuse intervention.

Doel van het onderzoek

AAA is a common disease and a major cause of death due to rupture. Preventive surgical aneurysm repair is
costly and associated with considerable morbidity and mortality. Doxycycline has been shown to attenuate the
expansion of aneurysm in animal models of AAA and results from two small clinical trials show that 12 months
doxycycline treatment is well tolerated and may arrested AAA growth.

We hypothesize that standard dose doxycycline treatment is a cost effective and well-tolerated means of stabilizing
AAA. Thus providing a pharmaceutical means of stabilizing AAA, and reducing the need for AAA repair.

Onderzoeksopzet

Baseline measurements, follow up at 6 months (6, 12 and 18 mo)

Onderzoeksproduct en/of interventie

Doxycycline 100mg or placebo daily, 18 mo

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Patients under surveillance with small aneurysms (i.e. 3.5-5.0 cm), and in larger AAA in patients who are unfit for or refuse open operation or endovascular intervention of their larger AAA (i.e. exceeding 5.0 cm).

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Unable to comply with follow up.

2. Contra-indications for doxycycline:

- known impaired liver function (ALAT >3-fold normal values)

- known renal failure (estimate clearance below 40 ml/min)

- excessive sun exposure.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-07-2008
Aantal proefpersonen:	300
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	16-06-2008
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1297
NTR-old	NTR1345
Ander register	: P07.152
ISRCTN	ISRCTN wordt niet meer aangevraagd

Resultaten

Samenvatting resultaten
N/A