The association between the 5-LO pathway & abdominal aortic aneurysms.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON25221

Source
NTR

Brief title
5-LO pathway

Health condition

patients with a small abdominal aneurysm of the aorta.

Intervention

Outcome measures

Primary outcome

1. The relation between LT levels (in stimulated neutrophils and urine) and annual rate of expansion of small AAAs.

2. Comparison of LT levels between subjects with AAA and normal controls.

3. The association between at-risk gene variant genes involved in 5-LO pathway and AAA growth rate. (4) To assess the presence of neutrophils and 5-LO products in AAA specimens

Secondary outcome

The relation between other inflammatory markers. (e.g. MMP9, hsCRP, MIP-1a, RANTES, MCP-1, CD-40L) and rates of expansion of small AAAs

Study description

Background summary

Inflammation and atherosclerosis
Atherosclerosis is a progressive arterial inflammatory disease, which ultimately may culminate in plaque rupture, fissure or erosion with subsequent thrombotic sequelae.
In this course, inflammatory mediators have been recognized to play a significant role. Thus, interactions between infiltrating and arterial wall cells, as well as cross-talk between resident tissue cells, may confer increased plaque vulnerability. More recently, the focus of cardiovascular prevention has gradually shifted from early detection of vulnerable plaques to identification of systemic and local factors that may adversely affect plaque stability and thus ease the onset of clinical events. These factors may add prognostic value to current risk stratification engines and/or serve as a target for pharmacological treatment. Over the last decades, a number of inflammatory mediators have been associated with increased cardiovascular risk. Among these, C-reactive protein is considered one of the most potent mediators. There is now compelling evidence, mostly from in vitro studies, that CRP may actually be a direct partaker in atherosclerosis progression rather than a risk marker solely. Recently, we showed in humans that infusion of CRP perturbs endothelial function and evokes inflammatory as well as procoagulant responses particularly under hypercholesterolemic conditions 1. Last, systemic inflammatory disorders in various clinical settings, ranging from infectious to auto-immune diseases, have been linked to accelerated atherogenesis. Consequently, the concept of inflammatory-driven atherogenesis has matured into an area of intensive research, with as ultimate goal that newly identified inflammatory mediators may represent important targets for prevention and treatment of cardiovascular disease.

The leukotriene pathway and atherosclerosis

Recently, the role of the leukotrienes (LT) produced by various cells has increasingly been recognized in the pathogenesis of atherosclerosis, including MI and stroke 2-5. LTs represent potent inflammatory lipid mediators and were originally identified on the basis of their contractile properties for bronchial SMC in asthma inflammation. For their production, free arachidonic acid, that is transported to the 5-lipoxygenase (5-LO) enzyme by the 5-LO-activating protein (FLAP) is converted to the unstable intermediate LTA4 and subsequently to LT end-products (ie. LTB4 or cysLTs such as LTC4 and LTD4). LTs function through B-LT and cysLT receptors. Variants of the genes encoding for proteins involved in the genesis of leukotriene mediators, such as LTA4 hydrolase 6 and FLAP 7 have been shown to confer risk of acute cardiovascular events. With regard to the latter, risk variants may increase the risk of MI up to 2-fold. Further, isolated neutrophils from MI patients have been shown to produce more LTB4 after stimulation than neutrophils from controls 8. Noticeably, there was a clear

association between increased LT production and the at-risk haplotype. LTs have been implicated in increased vasopermeability, chemotaxis, vascular adhesion of leukocytes and regulation of neutrophil function 9-12. These 5-LO derived products have also been shown to promote vascular SMC proliferation and endothelium-dependent vasoconstriction 13-16. The identification of neutrophils in atherosclerotic plaques associated with unstable angina pectoris and acute myocardial infarction suggests that neutrophils play a role in mediating destabilization of the atherosclerotic plaque 17. In advanced human atherosclerotic lesions, increased expression of the 5-LO pathway has been detected in co-presence of activated neutrophils 18. Last, LTs may promote expression and activation of the enzyme myeloperoxidase (MPO), generating potent lipid oxidants with ensuing accelerated consumption of NO 17;19;20. In both homozygous LDL receptor knockout and apoE deficient mice, a 35-day treatment with a LTB4 receptor antagonist resulted in retarded lesion progression as demonstrated by reduced lesional area and, concomitantly, decreased lipid accumulation and monocyte infiltration 21. Last, in patients with specific at-risk variants of 2 genes in the leukotriene pathway (in the FLAP and LTA4 hydrolase gene), 4-weeks treatment with DG-031 a FLAP inhibitor led to significant and dose-dependent suppression of biomarkers that are associated with increased risk of MI events 22 .Overall, these data thus far suggest that strategies that target this LT pathway may prove useful for primary and secondary prevention of cardiovascular events.

Study objective

Rationale: Accumulating evidence suggests that increased generation of leukotrienes (LT) by the 5-LO pathway may have direct actions on the vessel wall, particularly the adventitia, in the evolution of abdominal aortic aneurysm (AAA). Augmented inflammatory activity may further weaken the arterial wall, which may result in rapid expansion of the AAA and ultimately rupture. Thus, circulating and/or urinary levels of LT may serve as a novel biomarker for monitoring small asymptomatic AAA and may be an useful predictor of aneurysmal expansion. We hypothesize that (1) LTs produced by the 5-LO pathway are adversely implicated in the progression of AAA and (2) certain 5-LO pathway associated haplotypes (eg. spanning the LT4h gene or FLAP) may be associated with rapid expansion of AAA.

Intervention

patients with an asymptomatic, small aneurysm of the abdominal aorta and healthy male volunteers will visit the hospital 4 times during two years, at an interval of 6 months. During the first visit, patients will undergo a short physical examination, blood sampling, and ultrasound scanning for measurement of the maximum anterior-posterior diameter of the abdominal aorta. During the follow up visits patients will be subjected only to ultrasound scanning. Except for blood sampling related inconvenience (eg.hematomas) there are no risks associated with participation. In addition, there are no direct benefits for subjects participating in this study.

Contacts

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Eligibility criteria

Inclusion criteria

presence of asymptomatic, small AAA, older than 20 years, male or female

Exclusion criteria

1. A clinical condition which is actual and may interfere with the endpoints of the study (e.g. malignancy, infection/sepsis, chronic inflammatory disease).

2. The use of drugs with anti-inflammatory properties including prostaglandin synthetase inhibitors, which have been shown to reduce the inflammatory response

3. The use of immunosuppressants, including glucocorticoids, cyclosporine e.g.

4. Ruptured/symptomatic AAAs

Study design

Design

Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2006
Enrollment:	200
Type:	Anticipated

Ethics review

Positive opinion

Date:	26-09-2006
Application type:	First submission

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
NTR-new	NL770
NTR-old	NTR781

Register	ID
Other	: 1
ISRCTN	ISRCTN03932642

Study results

Summary results
N/A