Effect of Adalimumab on Inflammatory Activity in Atherosclerotic Lesions in Patients with Reumatoid Arthritis

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Primary: to compare inflammatory activity in atherosclerotic lesions between patients with active RA and controls, and to address the potential of anti-inflammatory therapy to reduce inflammatory atherosclerosis in RA patients.Secondary: 1] to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON41532

Source
ToetsingOnline

Brief title
Adalimumab and Inflammation of Atherosclerotic Lesions

Condition

- Autoimmune disorders
- Lipid metabolism disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Arthritis; Inflammatory Arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Jan van Breemen Instituut/Reade

Source(s) of monetary or material Support: Ministerie van OC&W,Reade (Jan van Breemen Instituut)

Intervention

Keyword: 18-FDG-PET/CT, Adalimumab, Atherosclerosis, Rheumatoid Arthritis

Outcome measures

Primary outcome

1] baseline difference in 18-FDG uptake in large arteries using Positron

Emission Tomography in RA patients versus controls.

2] changes in 18-FDG uptake in large arteries induced by methotrexate and

adalimumab (Humira) in a 3-4 month treatment window

Secondary outcome

1] changes in IMT 6, 12 and 24, 36, 48 and 60 months following

anti-inflammatory treatment with methotrexate or adalimumab (Humira)

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic inflammatory disease which has been associated with a sharply increased risk of cardiovascular disease (CVD) and CVD-associated mortality. The pathobiology of this increased risk is largely unknown. Traditional cardiovascular risk factor only partly explain the CVD risk in these patients, suggesting that chronic inflammation itself contributes to atherosclerotic plaque development and/or instability. Strategies to reduce cardiovascular risk in RA include modification of traditional risk facors (e.g. antihypertensive treatment, cholesterol lowering agents), as well as anti-inflammatory treatment. Direct evidence that anti-inflammatory treatment reduces CVD risk in RA is limited. Methotrexate, for example, appears to be associated with reduced CVD risk(1), but randomised clinical trials to provide high-grade evidence are lacking.
An intriguing hypothesis to explain the increased CVD risk is that the chronic

inflammatory state in RA enhances inflammation in atherosclerotic lesions. Circulating pro-inflammatory cytokines, for example, may activate inflammatory cells in atherosclerotic plaque. Limited evidence collected to date indeed suggests that RA patients have an increased propensity to shown more pronounced inflammation in atherosclerotic leasions.(2) Atherosclerosis is caused by several mechanisms of which chronic arterial wall inflammation is the driving force.(3) The biological composition and especially inflammatory state of an atherosclerotic plaque, rather than the degree of stenosis, are the major determinants of acute clinical events.

18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) has recently emerged as a promising modality for quantification of plaque inflammation. Evidence collected to date indicates that this method is reproducible, valid and responsive to treatment effects. Particularly in the regions of the aortic arch and carotid arteries, PET provides reproducible 18-FDG uptake quantification.(4;5) The degree of 18-FDG uptake in these regions has been shown to correlate with histopathological measures of plaque inflammation, which in turn correlate with CVD risk.(6) Apart from the background knowledge of the importance of inflammtion in inducing plaque instability, the applicability of this concept to 18-FDG uptake was recently confirmed in a study showing that 18-FDG-uptake in atherosclerotic lesions was the strongest predictor of CVD events.(7) In this study, 18-FDG uptake by large outweighed the predictive value of calcified lesions, providing further support for a crucial role of inflammation in plaque, and for 18-FDG-PET to detect this inflammation. Finally, preliminary evidence suggests that 18-FDG-PET quantification of plaque inflammation also is a variable which responds to treatment, as evidenced by reduction in 18-FDG uptake in carotid vessels following treatment with simvastatin.(8)

There is accumulating evidence for an increased carotid intima media thickness (cIMT), a well established marker for subclinical atherosclerosis, in RA patients in comparison to controls. A recent meta-analysis of the 22 controlled investigations revealed a 0.09 mm cIMT increase in RA in comparison to controls (9). However, this increase is smaller than expected in view of the doubled CVD risk in RA. This observation fits in the above-mentioned hypothesis that plaques might be

more prone to rupture due to the inflammatory state. Moreover, there are some suggestions from the literature for an impressive reduction of the cIMT when TNF blocking agents are administered.(10,11) This effect was not observed with MTX. However, these two studies suffer from a poor design and obviously a methodological sound styd is still required.

In summary, RA causes CVD presumably in part through plaque inflammation, plaque inflammation can be imaged by 18-FDG-PET, and the effects of anti-inflammatory treatment on plaque inflammation are unknown. These considerations provide a rationale for studying the effects of anti-inflammatory treatment on inflammation as a crucial aspect of plaque phenotype. In addition, effects of antiinflammatory agents on intima-media thickness may provide additional information on plaque burden.

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(9)***Van Sijl, Peters MJL, Knol DL, de Vet HC, Gonzalez-Gay MA, Smulders YM, et al. Carotid Intima Media Thickness in Rheumatoid Arthritis as Compared to Control Subjects Sem Arthritis Rheum 2010. [Epub ahead of print]
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(11) Ferrante A, Giardina AR, Ciccia F, Parrinello G, Licata G, Avellone G et al.Long-term anti-tumour necrosis factor therapy reverses the progression of carotid intima-media thickness in female patients with active rheumatoid arthritis. Rheumatol Int. 2009 Apr 23. [Epub ahead of print]

Study objective

Primary:
to compare inflammatory activity in atherosclerotic lesions between patients with active RA and controls, and to address the potential of anti-inflammatory therapy to reduce inflammatory atherosclerosis in RA patients.

Secondary:
1] to identify clinical and biochemical determinants of inflammatory activity in atherosclerotic lesions in RA patients
2] to compare the potential of methotrexate and anti-TNF treatment with adalimumab (Humira) to reduce inflammatory atherosclerosis
3] to assess the potential of anti-inflammatory drugs to reduce intima-media thickness

Study design

After recruitment at the outpatient clinics all patients will be invited to undergo baseline examination at the VUmc, which will include history, physical examination, ECG, ultrasound examinations, blood- and urine collection and 18-FDG-PET. Afterward, the patients in whom adalimumab (Humira) is indicated will start with the prescribed treatment as soon as possible. The patients in the control group will be followed at the outpatient clinic by their regular rheumatologist. Follow-up 18-FDG-PET will be performed 3-6 months after initiation of therapy. Changes in cIMT will be assessed after 6 and 12 months following anti-inflammatory treatment with methotrexate or dalimumab (Humira) and in individuals with osteoarthritis. Also, changes in IMT will be assessed after 24, 36, 48 and 60 months following adalimumab (Humira).
If a participant does not qualify any more for study participation, such as when a participant using adalimumab (Humira) is bound to switch to another drug due to therapy failure or side-effects, these participants will be excluded out the study, but will be taken into account in post-hoc intention-to-treat analyses.

Study burden and risks

18-FDG-PET-scan will be performed twice within a 3-4 month period. Chances for allergic reactions or spurious findings on scanning are extremely low and therefore the burden for patients minimal.
At each visit, participants will be asked about medication use, functional status, pain and will be physically examined for swollen and tender joints and blood pressure. Also, blood will be drawn from which levels of inflammatory markers, lipids, glucose and insulin will be determined (for which patients will need to be in a fasting state). Furthermore, an ultrasound examination of the carotid arteries will be performed at each visit.

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

- Age older than 45 years
- Both males and females
- Patients with active RA (DAS28 score >4.0)

Exclusion criteria

- Hypersensitivity to the active substance or to any of the excipients.'
- Gebruik van corticosteroiden
- Zwangerschap of zwangerschapswens
- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections.
- Moderate to severe heart failure (NYHA class III/IV)
- Cancer, limited life expectancy <12 months

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-09-2011
Enrollment:	95
Type:	Actual

Ethics review

Approved WMO Date:	23-12-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-04-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	03-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2015
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
CCMO	NL34047.048.10

Study results

Date completed:	10-07-2020
Actual enrolment:	90