Effects of adalimumab on biomarkers in synovial tissue in patients with rheumatoid arthritis

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Primary objective:to study changes in synovial inflammation and cytokine expression in serial biopsy samples following the administration of adalimumab in patients with active rheumatoid arthritis.Secondary objectives: (i) assess clinical response...

Ethical review	Approved WMO
Status	Pending
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON30623

Source
ToetsingOnline

Brief title
Geen verkorte titel

Condition

- Autoimmune disorders
- Joint disorders

Synonym
Rheumatoid arthritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: anti-TNF alpha therapy, biomarkers, rheumatoid arthritis, synovial tissue

Outcome measures

Primary outcome

Analysis of the changes in the cellular infiltrate and the expression of

cytokines will be performed by immunohistochemical staining, analyzed by

digital image analysis

The following biomarkers will be assessed:

* CD3 (T-cell marker)

* CD4

* CD8

* CD22 (B-cell marker)

* CD68 (macrophages)

* CD163 (resident tissue macrophages)

* MRP8 (S100A8, infiltrating macrophages)

* MRP14 (S100A9, infiltrating macrophages)

* CD38 (plasma cells)

* CD55 (fibroblast like synoviocytes)

* CD15 (neutrophils)

* IL-1

* IL-6

* TNFalpha

* Tweak/ Fn14

Secondary outcome

The endpoint of clinical efficacy will be evaluated at week 8 and week 16 after start of adalimumab therapy. Clinical response will analysed by the change in DAS28 score and according to the EULAR response criteria.

Immunohistochemistry and PCR analysis of the following cytokines in the peripheral blood and synovial tissue will be performed

Tissue samples and peripheral blood will be stored for future microarray and PCR-analysis.

Cellular reactions of the synovial cells measured by cytokine production in fresh synovial biopsies before and after treatment will be assessed.

Study description

Background summary

Although the etiology of rheumatoid arthritis (RA) remains elusive, immune-mediated mechanisms are known to be of crucial importance. Since the synovial tissue is the target tissue of this disease, pathogenetic mechanisms are best studied in this type of tissue. Technical developments have made it possible to obtain synovial tissue in a relative easy way, by performing a mini-arthroscopy of an inflaed joint on an outpatient basis. This technique has been proven effective and safe.
TNF blocking agents have been a breakthrough in the treatment of rheumatoid arthritis since their introduction more then ten years ago. Although very effective, the exact mechanism of action in the inflamed synovial tissue of RA patients is not well known. In this study, we want to study the changes in the inflamed synovial tissue of RA patients, when they receive anti-TNF treatment

for their disease.

Study objective

Primary objective:
to study changes in synovial inflammation and cytokine expression in serial biopsy samples following the administration of adalimumab in patients with active rheumatoid arthritis.

Secondary objectives:
(i) assess clinical response.
(ii) compare immunohistochemical analysis and Polymerase Chain Reaction (PCR) analysis of cytokines in tissue samples, and changes in gene expression in synovial tissue and peripheral blood by microarray analysis will be assessed.
(iii) cellular responses of synovial explants to pro-inflammatory stimuli and/or antagonists will be studied.

Study design

Following a screening period of 2 weeks, patients will be enrolled into a prospective study of 16 weeks. Synovial biopsies from an actively inflamed joint (knee or ankle) will be obtained by mini-arthroscopy before administration of adalimumab and at week 8 of treatment. The serial biopsies are obtained from the same joint. The baseline visit and first arthroscopy must be within 3 days before the first administration of adalimumab.

Patients are allowed to use concomitant non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (prednisone equivalent * 10 mg/day) and methotrexate (5 -30 mg/week), provided the dose has been stable for at least 4 weeks prior to baseline.

Clinical evaluation of joint pain and swelling will be repeated after 4, 8, and 16 weeks of treatment. Patients will be seen for efficacy and safety assessments in accordance with standard guidelines for clinical practice during the entire study.

In total there will be 5 study visits: screening, baseline, week 4, week 8 and week 16.
There will be a ± 3 day deviation for all return visits. All visits will be fixed with reference to the baseline visit.

Intervention

Patients will be treated with adalimumab (Humira) subcutaneously every other week, according to the manufacturers guidelines. Before and after 8 weeks of treatment, they will undergo a mini-artroscopy on an outpatient basis.

Clinical evaluation will take place at several visits.

Study burden and risks

After signing informed consent, patients will undergo a screening visit. During this visit medical history and medication will be assessed. A physical exam, including a joint count will be done. The patient has to fill out questionaires about the effects of the disease on daily activities.

After enrolment, 4 visits will be performed until week 16. During these visits, joint counts and questionaires will be assessed to determine the disease activity. These visits will take roughly one hour of the time of the patient. During these visits, blood will be drawn, a total of 190 ml in 16 weeks of study (about 38 ml per visit). If the patient has a good response at week 16, the medication will be continued.

Mini-arthroscopy will take place at baseline and after 8 weeks. This procedure is relatively safe, with a risk of complications of less than 0.3%.

Patients will be treated with anti-TNF therapy according to the Dutch guidelines.

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

Disease Activity Score (DAS) 28 ><= 3.2
Be > 18 years of age and <85 years.
Use concurrent methotrexate treatment (5 - 30 mg/week; stable for at least 28 days before study enrolment) during the study. Subjects may be taking nonsteroidal anti-inflammatory drugs, provided the dose and frequency have been stable for at least 28 days. Subjects may be receiving prednisone therapy * 10 mg/day provided that the dosage has been stable for at least 1 month prior to entry.

Exclusion criteria

A history of or acute inflammatory joint disease of different origin e.g. mixed connective tissue disease, seronegative spondylarthropathy, psoriatic arthritis, Reiter*s syndrome, systemic lupus erythematosus or any arthritis with onset prior to age 16 years
Acute major trauma
5)Therapy within the previous 60 days with:
* any experimental drug
* alkylating agents, e.g. cyclophosphamide, chlorambucil
* antimetabolites
* monoclonal antibodies
* growth factors
* other cytokines
Therapy within the previous 28 days with:
* parenteral or intraarticular corticoid injections
* oral corticosteroid therapy exceeding a prednisone equivalent of 10 mg daily
* present use of DMARDs other than methotrexate
Fever (orally measured > 38°C), chronic infections or infections requiring anti-microbial therapy
Other active medical conditions such as inflammatory bowel disease, bleeding diathesis, or severe unstable diabetes mellitus
Manifest cardiac failure (stage III or IV according to NYHA classification)
Impaired coagulation
A congenital or acquired immunodeficiency, a history of cancer or lymphoproliferative disease or treatment with total lymphoid irradiation.
* (The known HIV-positive status may be defined either by a positive blood test or clinical diagnosis.)

Platelet count less than 100 x 109/l
Inability to give informed consent
Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2007
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Humira
Generic name:	Adalimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Application type:	First submission
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	EUCTR2006-006895-39-NL
CCMO	NL15835.018.07