Effects of abatacept (Orencia®) on biomarkers in synovial tissue in patients with rheumatoid arthritis

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

Summary

ID

NL-OMON34549

Source
ToetsingOnline

Brief title
Effects of abatacept on synovial tissue in RA

Condition

- Autoimmune 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: abatacept, biomarkers, rheumatoid arthritis, synovial tissue

Outcome measures

Primary outcome

Changes in synovial inflammation in serial biopsy samples following the

administration of abatacept in patients with active rheumatoid arthritis.

Secondary outcome

clinical response

cellular responses of synovial explants to inflammatory stimuli, and/or

antagonists, before and after treatment with abatacept

synovial biomarkers predictive of the clinical response to abatacept treatment

the changes in phenotypes of peripheral blood mononuclear cells (PBMCs)

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic and progressive inflammatory disease marked by infiltration of synovial tissue by activated lymphocytes, dendritic cells (DC) and macrophages, and proliferation of stromal fibroblast-like synoviocytes (FLS). Interactions between activated lymphocytes and other cells in synovial tissue play an important role in the perpetuation of RA pathology. Current therapies provide only partial protection against inflammation and joint destruction, and not to all patients. Therefore, increased knowledge of the molecular basis of RA and the working mechanism of therapeutic compounds is necessary for the analysis of their efficacy and rational application in the clinic. Abatacept, a human recombinant soluble fusion protein, composed of the extracellular domain of CTLA-4 and a mutated IgG1 Fc fragment, has shown a remarkable efficacy in clinical trials in patients with RA. Abatacept is proposed to work by interfering with the interaction of CD28 on T cells with its ligand CD80 or CD86 on antigen presenting cells.This ligation lowers the treshhold for T cell receptor activation. However, T-cell function in abatacept clinical trials has never been studied and there is no direct evidence that the

T cell receptor is actively engaged in RA synovial T cells.

Understanding the mechanism of action of Abatacept in RA will need to consider not only the potential effects of this compound on classical TCR costimulation and T cell activation, but also possible direct and indirect effects on B cells and other cells expressing CD80/86 in the synovial tissue, such as T cells, monocyte/macrophages, and DCs. We have some preliminary data from a previous study suggesting that B cells and macrophages (antigen presenting cells decrease after therapy with abatacept and that the T cells stay unaffected. The aim of this study is to expand these immunohistochemical data and to study changes in cytokine production of ex vivo stimulated synovial biopsies after treatment, in order to identify the mechanism of action of abatacept.

Study objective

The primary objective is to study changes in synovial inflammation in serial biopsy samples following the administration of abatacept in patients with active rheumatoid arthritis.
The secondary objectives of this study are to
(I) assess clinical response
(II) assess cellular responses of synovial explants to inflammatory stimuli, and/or antagonists, before and after treatment with abatacept
(III) identify synovial biomarkers predictive of the clinical response to abatacept treatment
(IV) investigate the changes in phenotypes of peripheral blood mononuclear cells (PBMCs)

Study design

Following a screening period of 2-3 weeks, patients will be enrolled into a prospective open label study for a period of 24 weeks. Synovial biopsies from an actively inflamed joint (knee, ankle or wrist) will be obtained by mini-arthroscopy or ultrasound guided biopsy before administration of abatacept and at week 16 of treatment.

Clinical evaluation of joint pain and swelling will be done at baseline and repeated after 4, 8, 12, 16 and 24 weeks of treatment. Patients will be seen for efficacy and safety assessments in accordance with standard guidelines for clinical practice.

In total there will be 9 study visits: screening, baseline, week 2, week 4, week 8, week 12, week 16, week 20 and week 24. There will be a ± 3 day deviation for all return visits. All visits will be fixed with reference to the baseline visit.

Intervention

ABATACEPT (ORENCIA) for 24 weeks
mini-artroscopy

Study burden and risks

The treatment of abatacept can cause side effects, although they are usualy mild.

Mini-artroscopy:

Mostly, the arthroscopy is performed without complaints. However, a small risk exists of complications, such as joint infection
(< 0,3%) . Carefully cleaning the skin and the use of sterile gloves minimize the change of getting an infection. The joint can also be stiff a few days after the arthroscopy. Reactions to local anesthesia can occur but disappear quickly.

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

Males and females with a diagnosis of active rheumatoid arthritis (with a DAS28 CRP > 3,2) who have failed MTX therapy, with an inflamed knee, ankle or wrist joint.

Exclusion criteria

Pregnancy, breastfeeding
subjects who are impaire, incapacitated or incapable of completing study related assessments
subjects who meet diagnostic criteria for any other rheumatic disease (e.g. lupus erythematous)
subjects who have previously received treatment with an investigational biologic RA therapy, antie-TNF theray, rituximab, tocilizumab or abatacept
subjects with active vasculitus of a major organ system with the exception of rheumatoid nodules
Subjects with current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, neurological, or cerebral disease, or other medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
Subjects with a history of cancer within the last five years (other than nonmelanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to dosing.
Subjects who have clinically significant drug or alcohol abuse.
Subjects with any serious bacterial infection within the last 3 months, unless treated and resolved with antibiotics, or any chronic bacterial infection (such as chronic pyelonephritis, osteomyelitis and bronchiectasis).
Subjects at risk for tuberculosis (TB). Specifically, subjects with:
a) A history of active TB within the last 3 years even if it was treated
b) A history of active TB greater than 3 years ago unless there is documentation that the prior anti-TB treatment was appropriate in duration and type
c) Current clinical, radiographic or laboratory evidence of active TB
d) Latent TB which was not successfully treated
Subjects with herpes zoster or cytomegalovirus (CMV) that resolved less than 2 months prior to signing informed consent.
Subjects with evidence (as assessed by the Investigator) of active or latent bacterial or viral infections at the time of potential enrollment, including subjects with evidence of Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C infection detected during screening.

Subject who have received any live vaccines within 3 months of the anticipated first dose of study medication or who will have need of a live vaccine at any time following Day 1 of the study

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2010
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	06-12-2010
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	EUCTR2010-021435-14-NL
CCMO	NL32939.018.10