Differential effect of adalumimab versus etanercept on apoptosis in the psoriatic skin

Published: 02-05-2007
Last updated: 24-08-2024

We hypothesized that one of the key mechanisms explaining the differences in effect between adalumimab and etanercept on psoriatic skin is that adalumimab, by being a monoclonal antibody like infliximab, is a better inducer of apoptosis resulting in...

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

Summary

ID

NL-OMON30655

Source
ToetsingOnline

Brief title
Adalumimab versus etanercept; apoptosis in the psoriatic skin

Condition

- Autoimmune disorders
- Joint disorders
- Skin and subcutaneous tissue disorders NEC

Synonym
arthritis psoriatica

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Abbott,unrestricted grant ABBOTT

Intervention

Keyword: adalumimab, etanercept, psoriasis, TNF-alpha

Outcome measures

Primary outcome

Primary

1. Amount of apoptotic cells

2. Evaluation of cellular infiltrates

Secondary outcome

Secondary

1. Clinical improvement; DAS response criteria, PASI skin score.

Study description

Background summary

Differential effect of adalumimab versus etanercept on apoptosis in the psoriatic skin

Psoriatic arthritis (PsA) is an auto inflammatory disease characterized by inflammation of both skin and joints. The most common form of psoriasis is plaque psoriasis. Although psoriasis is characterized by thickening of the epidermis, the immune system has a prominent role in the development of the disease. Psoriatic skin is characterized by hyperproliferation of keratinocytes which is regulated by cell proliferation, cell influx and programmed cell death / apoptosis(1). T-cells and macrophages are also present in the inflamed skin. Keratinocytes, dendritic cells, T-cells as well as macrophages in skin all can produce TNF-α. TNF-α is found at particular high concentrations in the skin lesions and plasma of patients with psoriasis(2-4).
TNF-α is a multifunctional cytokine belonging to the TNF-superfamily of ligands and receptors. TNF-α can induce a proliferative response characterized by cell growth and differentiation, but can also induce programmed cell death and apoptosis or cellular necroses. Which effect dominates depends on celltype, the TNF receptor involved (receptor 1 and/or 2), and the subsequently activated

intracellular signaltransductionroutes(5).
In vitro studies showed that TNF-α stimulates keratinocyt proliferation. Binding of TNF-α with it*s receptor leads to further keratinocyt proliferation and induction of syntheses of pro-inflammatory cytokines like IL-6 en IL-8 and induces the up regulation of adhesionmolecules, with subsequent T-cell migration to the skin. For this migration the T-cell needs interation respectively between; CLA (cutaneous lymphocyte antigen) and E-selectine, chemokines and their chemokine receptor, and LFA-1 (leukocyte function associated antigen-1) and intercellular adhesionmolecule-1 (ICAM-1) on the dermal postcapillary venules (1).

Besides this important role for TNF-α in cellular activation and induction of adhesion molecules, TNF-α also is an important inducer of apoptosis(6). Apoptosis or programmed cell death is a natural process which is essential for the homeostasis of the human body. During apoptosis all kind of intracellular changes take place characterized by blebbing of the cell membrane and changes in the colour and shape of the nucleus. Apoptosis of the cell is followed by a fast receptor mediated phagocytosis of tissue macrophages.
Inhibition of this process leads to an increase in the number and longevity of keratinocytes as seen in psoriatic arthritis. In the psoriatic skin an aberrant expression has been found of molecules involved in the apoptotic process. The present markers suggest a suppression of the apoptotic process(7;8). Bcl-2 and associated proteins such as Bax en Bcl-xl, modulate the apoptotic process (6) . Bcl-2 is anti-apoptotic and Bax is pro-apoptotic. In the psoriatic skin an increase has been found of the anti-apoptotic (9)It has been shown that inhibition of TNF-α has an excellent effect on skin lesions in PsA. Patients with severe psoriasis of the skin are almost fully cured(10-12).The exact mechanisms involved are at present unclear. One study showed that, the degree of apoptosis in the skin of patients with PsA before and after treatment with infliximab (TNF-α blocking antibody) did not change. As expected there was almost no apoptosis before treatment, and also, which was unexpected 48 hours after treatment(13). This in sharp contrast with studies done in Crohn*s disease in which large amounts of apoptotic T-lymphocytes can be found 24 hours after treatment with infliximab(9). One of the explanations for the differences found, between the two studies, could be that the skin biopsies in the first study were taken 48 hours after start of treatment. This could be to late to study apoptosis. In a recent study done in rheumatoid arthritis (RA) both infliximab as well as etanercept (soluble TNF receptor fusion protein) induced apoptosis of macrophages but, not of T-cells(14). Apoptosis was seen in cultured monocytes 24 hours after treatment and in synovial biopsies taken from involved joints up to 8 weeks after treatment. This in contrast to the findings in Crohn*s disease in which infliximab induces no apoptosis of monocytes / macrophages only of T-cells(15;16). Several reports indicated that adalumimab (a fully human monoclonal directed against TNF-α) is superior to etanercept with respect to the skin lesions as seen in PsA(17;18). The exact pathogenesis involved has not been studied so far.

Study objective

We hypothesized that one of the key mechanisms explaining the differences in effect between adalumimab and etanercept on psoriatic skin is that adalumimab, by being a monoclonal antibody like infliximab, is a better inducer of apoptosis resulting in a better effect on skin lesions in PsA.

Study design

Patients having active PsA with skin lesions despite treatment with etanercept and methotrexate, and no contraindications for TNF blockers, are eligible for the present study. PASI scores and DAS scores will be performed before and after therapy at 4 different time points.
Patients will be followed for three months, during the study, and continue on TNF blocking therapy when indicated after the study is finished.
Skin biopsies will be taken before and shortly after (2 biopsies) the start of adalumimab and processed for immune histochemistry. The biopsies will be stained with markers for different cell types (T-cells, macrophages, keratinocytes and dendritic cells) and markers for apoptosis (caspase 3) . Cellular infiltrates and apoptotic cells will be scored on a numeric scale.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness.

The burden for the patient exists of three skin biopsies, extra control visits and the extra blood samples during regular blood sampling. There will be no direct benefit for the patient during the study. We hope that gaining insight in the mechanisms involved in psoriatic arthritis skin disease will help defining new effective treatment strategies.

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

1. Man and woman older than 18 year en younger than 75 year
2. Diagnosis of Psoriatic arthritis with involvement of the peripheral joints
3. Failure on etanercept therapy as measured by PASI and DAS
4. Indication for treatment with etanercept according to the LABAG guidelines
5. Active disease despite treatment with methotrexate and etanercept, MTX >_ 15 mg/wk in a stable dosis during 3 months; still active skin lesions despite MTX and etanercept treatment
5. Corticosteroids (max 10 mg/day) en NSAID*s stable dose.
6. Signed informed consent.

Exclusion criteria

1. Rheumatoid arthritis and/or other autoimmune diseases
2. Pregnancy / breastfeeding.
3. TBC/ hepatitis b or c or other chronic infections.
4. Contraindications for TNF-alpha like a malignancy or a chronic demyelinating disease.
5. No participation in another study.
6. No PUVA or vitamine D treatment during 1 month before and during the study.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-05-2007
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Enbrel
Generic name:	etanercept
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Humira
Generic name:	adalumimab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	02-05-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2007-000136-45-NL
CCMO	NL14891.042.07