ANTI-IGE THERAPY (OMALIZUMAB) IN IGE-ACPA POSITIVE RHEUMATOID ARTHRITIS
Addendum: An open label extension study to provide continuation of anti-IgE therapy to Rheumatoid Arthritis patients who participated in the TIGER study
P10.161

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- To evaluate the safety and efficacy of anti-IgE therapy with respect to:Clinical disease activity (DAS44), laboratory parameters and adverse events. - To evaluate whether disease activity correlates with immunological parameters, including...

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

Summary

ID

NL-OMON37983

Source
ToetsingOnline

Brief title
TIGER (Trial of anti-IgE in RA)

Condition

- Autoimmune disorders
- Joint disorders

Synonym
rheumatism, rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: medicatie wordt gratis geleverd door Novartis,Novartis

Intervention

Keyword: ACPA, Anti-IgE, Rheumatoid Arthritis

Outcome measures

Primary outcome

1. Clinical parameters for disease activity are measured by the DAS44 (Disease

Activity Score on 44 joints) assessment. Responses are classified as follows:

- Complete response is defined as a DAS44 improvement of > 1.2 and DAS<2.4

- Moderate response is defined as DAS44 improvement of 1.2 and DAS >2.4:

OR

DAS 44 improvement of >0.6 en <=1.2 and DAS <=3.7:

- Non-response is defined as DAS44 improvement of >0.6 en <=1.2 improvement

and DAS >3.7

OR improvement of <=0.6

2. Immunological parameters in peripheral blood and synovium after treatment

with anti-IgE antibodies (omalizumab) are:

- proportion of peripheral blood basophils, mast cells in synovium

- functional presence of IgE-ACPA,

- IgE , FcERI expression on basophils, mast cells, B cells and DC

- synovial infiltration of B cells, plasmacells, mast cells and (IgE-)ACPA

presence in synovial fluid

3. Safety and toxicity parameters are evaluated according to WHO Common

Toxicity Criteria

Secondary outcome

not applicable

Study description

Background summary

The discovery of antibodies against cyclic citrullinated proteins (ACPA) was a breakthrough. These antibodies are highly specific for RA and the occurrence of ACPA is observed several years before the onset of the disease.
Moreover, recent evidence was raised for a pathogenic role of ACPA: Fc*RI+ cells from ACPA+ RA patients can be directly activated by citrullinated antigens, using an ex vivo human model. These data show the ability of citrullinated proteins to crosslink IgE-ACPA specifically via Fc*RI and support a functional role of IgE-ACPA in ACPA+ RA patients.

Humanized anti-IgE antibodies have been developed for clinical use in asthma: rhuMAb-E25 or omalizumab has been successfully used for the treatment of allergic asthma. The mechanisms of action of human anti-IgE are diverse (12). First, it neutralizes IgE by binding to the constant region 3 of the heavy chain at a site that prevents IgE to bind to its receptors. Secondly, anti-IgE forms trimers and tetramers that sweep away antigens. Thirdly, by reducing free IgE by >99%, anti-IgE also markedly reduces the density of FcepsilonRI on mast cells, basophils and DCs. In conclusion, if IgE-ACPA are involved in disease progression in RA, this humanized blocking IgE antibody has great potential to benefit IgE-ACPA positive RA patients.

Study objective

- To evaluate the safety and efficacy of anti-IgE therapy with respect to:
Clinical disease activity (DAS44), laboratory parameters and adverse events.

- To evaluate whether disease activity correlates with immunological parameters, including immunopathology and IgE-ACPA-autoantibodies.

ADDENDUM:
1. To provide treatment with anti-IgE therapy to Rheumatoid Arthritis (RA) patients who participated in the original protocol of the TIGER study P10.161.

2. To assess the safety and tolerability of long term treatment with anti-IgE therapy in a clinical setting.

Study design

A randomized placebo-controlled double blinded single-center, phase IIa study investigating anti-IgE therapy (omalizumab) in IgE-ACPA positive rheumatoid arthritis patients.

ADDENDUM:
This is an open label extension study in IgE-ACPA positive RA patients who participated in the TIGER trial P10.161. After completion of visit 7 in the original study, patients who in the investigators clinical judgement would benefit from the anti-IgE treatment will be offered enrolment in this extension study.

Intervention

This investigation is a placebo-controlled randomized double blinded single-center phase IIa study, administering subcutaneously every four weeks 300 mg of monoclonal anti-IgE antibody or placebo in patients with IgE-ACPA positive RA during 6 months.

ADDENDUM:
During the open label extension study with IgE-ACPA positive RA, patients will be administered subcutaneously every four weeks 300 mg of monoclonal anti-IgE antibody during extra 12 months.
Treatment with omalizumab comprises the following :
At day 168 (Month 6), day 196 (M 7), day 224 (M 8), day 252 (M 9), day 280 (M 10), day 308 (M 11), day 336 (M 12), day 336 (M 13) M 14 M 15 M 16 M 17 M 18 patients receive a subcutaneous injection with 300 mg omalizumab during short stay at the clinic.

Study burden and risks

Risk for adverse events caused by omalizumab:
headache, nausea, unwelness, allergic reaction

Other risks:

Pain or hematome by venous punction or sucutaneous administering of medicine
Pain caused by arthroscopy

Discomfort caused by investigation procedures :
extra blood withdrawal during treatment with omalizumab /placebo.

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. Patients with refractory active rheumatoid arthritis (RA). Refractory disease is defined as persistent or relapsed disease activity despite conventional treatment, i.e. combination of disease modifying antirheumatic drugs including maximal tolerable doses of methotrexate. Active disease is defined as a DAS44 (Disease Activity Score of 44 joints) score of more than 3.6

2. Presence of IgE-ACPA
3. Age above 18 years
4. WHO performance status 0, 1 or 2
5. Informed consent according to rules and regulations of Leiden University Medical Center.
Addendum: Rheumatoid arthritis patients included in placebo controlled TIGER study during 6 months according to the inclusion and exclusion criteria (see original protocol P10.161) can be included in the open label extension protocol, regardless their previous treatment (omalizumab or placebo).

Exclusion criteria

1. History of allergic or anaphylactic reaction to any therapeutic agent or known hypersensitivity to any component of anti-IgE monoclonal antibodies or to murine proteins.
2. No previous therapy with corticosteroids or a biological agent during the last 3 months.
3 No previous therapy with rituximab, leflunomide
4. Life expectation of less than 6 months
5. History of severe CNS disturbances and psychiatric problems
6. Severe uncontrolled infections including parasitosis
7. Irreversible major organ dysfunction, defined by any of the following criteria:
- creatinine clearance < 40 ml/min.
- left ventricular ejection fraction < 40%;
- pericardial effusion with haemodynamic consequences.
- resting arterial oxygen tension (PaO2) < 8 kPa (<60 mmHg) and / or resting arterial carbon dioxide tension (PaCO2) > 6.7 kPa (>50 mmHg).
- sustained 3-fold increase in serum transaminase or bilirubin.
8. HIV positivity
9. Positive pregnancy test or unwillingness to use adequate contraception for the duration of the study
10. History of cancer, including solid tumors, hematological malignancies and carcinoma in situ (except for basal cell and squamous cell carcinoma of the skin that have been treated and cured).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2011
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xolair
Generic name:	omalizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-09-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-11-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-03-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-07-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO Date:	08-11-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	25-03-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2009-017306-36-NL
CCMO	NL33504.058.10
Other	NTR TC=2434