A Double Blind, Randomized, Placebo Controlled, Multi-Center Trial of Anti-TNFα Chimeric Monoclonal Antibody (infliximab, Remicade®) in Combination with Methotrexate in Patients with Very Early Inflammatory Arthritis (DINORA Study)

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The primary objective of the study is to demonstrate that patients with very early arthritis have a higher probability of achieving a state of clinical remission at end of infliximab therapy if treated with infliximab plus MTX when compared to MTX...

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

Summary

ID

NL-OMON31097

Source
ToetsingOnline

Brief title
DINORA: Definitive Intervention in New Onset Rheumatoid Arthritis

Condition

- Autoimmune disorders
- Joint disorders

Synonym

Rheumatoid arthritis-rheumatic disease

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Centocor Inc.

Intervention

Keyword: Early intervention, Infliximab, methotrexaat, Rheuamtoid Arthritis

Outcome measures

Primary outcome

Comparison of presence of clinical remission between treatment with infliximab plus MTX versus MTX monotherapy and supportive treatment only at end of infliximab therapy, i.e. at at least 2 consecutive visits after month 3 during the first 54 weeks.

Secondary outcome

Comparison, Group I versus Group II and Group III of:

* the presence of persistent clinical remission at week 106;

* the presence of persistent clinical remission at week 54 since start of therapy;

* the presence of persistent clinical remission at week 106;

* radiographic progression at week 22, 54 and 106;

* the presence of clinical remission at every time point during the trial;

* the presence of clinical remission by SDAI and CDAI at every time point during the trial;

* the presence of remission by Pinals criteria at every time point during the

trial

* the presence of near-remission (DAS28 < 2.6) at every time point during the

trial;

* the duration of clinical remission or near-clinical remission during the

entire trial;

* time to remission;

* time to relapse after withdrawal of infliximab therapy in patients who

achieved persistent clinical remission;

* all variables included in the WHO/ILAR core set for clinical trials

(66-joints swollen joint count, 68-joints tender joint count, pain, patient and

evaluator global assessments, health assessment questionnaire (HAQ), CRP, ESR)

at every time point during the trial;

* DAS28, SDAI, CDAI and RADAI at every time point during the trial;

* ACR 50 and 70 response, SF36, Fatigue (VAS) and Pharmacoeconomics at week 2,

6, 14, 22, 30, 38, 54, 70 and 106;

* glucocorticoid and NSAID/coxib dosage at every time point during the trial;

* number of visits at which relapse from remission was noted.

Study description

Background summary

The chronic erosive arthritides, among which rheumatoid arthritis (RA) is the most common disease, are characterized by inflammation of joints, tendons and tendon sheaths. In order to suppress the inflammatory activity and to retard or even stop the joint damage, disease modifying antirheumatic drugs (DMARDs) are used to treat patients with RA. Long-term clinical remission seems to be pivotal to stop the pathophysiological process underlying progressive joint

damage. Very early arthritis may be a manifestation of a spectrum of different diseases, with a heterogeneous outcome, but arthritis persistent for >12 weeks was prone to become RA.
To understand early arthritis and develop new treatment approaches, a number of investigators have both established early arthritis clinics (EAC) and conducted treatment trials which differ in the criteria for patients to be included, such as whether the patient had to fulfill classification criteria. However, there is a strong belief that starting treatment before patients fulfill the classification criteria for RA may be beneficial. If the goal is to prevent the evolution to RA in patients with very early inflammatory arthritis or prevent progressive inflammatory disease in all patients, it is essential to begin therapy early in the course and regardless of disease designation.
The primary hypothesis is that the development of persistent chronic arthritis (e.g. RA) can be prevented (durable state of remission, or even cure) if highly effective therapy (Infliximab plus MTX as compared to symptomatic therapy) is started during the earliest clinically perceptible phase of the disease shortly after the first signs of persistent arthritis.

Study objective

The primary objective of the study is to demonstrate that patients with very early arthritis have a higher probability of achieving a state of clinical remission at end of infliximab therapy if treated with infliximab plus MTX when compared to MTX monotherapy or supportive treatment only.

Study design

This is a double blind, randomized, placebo controlled, multi-center trial in 200 subjects

Intervention

200 subjects (80 per DMARD treatment arm and 40 in the supportive treatment arm) will be randomly assigned, stratified by glucocorticoid use to one of the following treatment groups:
Group I To receive symptomatic therapy as well as oral methotrexate and infliximab
Group II To receive symptomatic therapy as well as oral methotrexate and placebo infusions.
Group III To receive symptomatic therapy as well as placebo tablets and placebo infusions

Symptomatic therapy will consist of NSAIDs (or coxib) and, if deemed indicated, glucocorticoids at a dose of no more than 10mg/day of prednisone or equivalent dose (no MTX or other DMARDs). In addition, patients will receive proton pump inhibitors for gastric protection.

Total weekly dose for MTX or placebo tablets will be standardized throughout the protocol. MTX will be dosed orally, according to a rapid dose escalation scheme, as used previously in several clinical trials in early RA. In brief, MTX will be started at 10 mg/week, and increased to 25 mg/week in three steps with a 2 weeks interval, unless toxicity prevents such a strategy. If the patient goes into remission during the dose escalation period, escalation should be halted and the dose should be kept stable until patient is a primary success and until end of study treatments at week 54 (see section 9.4 for definition of remission). If remission is not sustained, dose escalation will be resumed.

Infliximab will be administered by intravenous infusions at a dose of 3 mg/kg at 0, 2 and 6 weeks, and at 5 mg/kg every 8 weeks thereafter.

To reduce MTX-related adverse events, all patients will receive folate supplementations (5mg/day on 2 days per week).

Study burden and risks

There are 18 visit during 2 years of study, blood is taken on every studyvisit. The time between 2 visits varies from 4 to 8 weeks. Each patient is treated with infliximab-placeboinfusions in week 1,2 and 6 of the study and after that every 8 weeks (max 9 infusions). A studyvisit will take 1 hour time and about 4 hours for a visit with an infusion of infliximab/placebo.

Possible risks to the patient are mainly associated with the toxicity of the drugs used in this study:
Infliximab:
-increased risk for tuberculosis and reactivation of hepatitis infection
-increased risk for infections
-skinrash
-changes in bloodpressure during infusion
More general adverse events:
-nausea, vomiting, stomache ache
-blood: decrease in leocicytes
-liver- and kidney function disturbance

Drawing blood and the infusions administered within the context of this clinical trial can lead to light pain and hemorrhages at the administration site.

The amount of radiation the patient will receive for the radiograph of the chest and for the hand and foot is within the recommended limits. The risk brought by these examinations can be classified as minimum.

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) Men and women, >= 18 and <= 75 years of age
2) The presence of arthritis:
a) Must be established in a rheumatology center,
b) Must be present in at least 2 joints of the 66 joint count
c) Without any previous episodes of inflammatory joint disease
3) Duration of symptoms :
a) Must be 2 weeks at least
b) Must be 16 weeks at most

Exclusion criteria

*previous treatment with corticoseroids or DMARD's
*positive tuberculosis test

Study design

Design

Study phase:	3
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):	01-11-2007
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Methotrexaat
Generic name:	Methotrexaat
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	remicade
Generic name:	infliximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-10-2007
Application type:	First submission
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	EUCTR2006-002787-26-NL
CCMO	NL19673.058.07
Other	volgt