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A double blind, randomised, placebo controlled, multicentre trial of Anti-Tumour Necrotising Factor alpha (Anti-TNFα) chimeric monoclonal antibody (infliximab, Remicade®) in combination with methotrexate in patients with very early inflammatory arthritis

Submission date
04/10/2007

Recruitment status
No longer recruiting

Registration date
18/12/2007

Overall study status
Completed

Last Edited
13/08/2018

Condition category
Musculoskeletal Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2006-002787-26

Protocol serial number
DINORA4

Study information

Scientific Title
A double blind, randomised, placebo controlled, multicentre trial of Anti-Tumour Necrotising Factor alpha (Anti-TNFα) chimeric monoclonal antibody (infliximab, Remicade®) in combination with methotrexate in patients with very early inflammatory arthritis

Acronym
DINORA

Study objectives
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 Methotrexate (MTX) when compared to MTX monotherapy or supportive treatment only.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethikkommission der Medizinischen Universität Wien und des Allgemeinesn Krankenhauses der Stadt Wien AKH, 04/07/2006, ref: EK 292/2006

Study design
Double blind randomised placebo controlled multi-centre trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Early inflammatory arthritis

Interventions
This is a double blind, randomised, placebo controlled, multi-centre trial in which a total of 89 subjects (36 per DMARD treatment arm and 17 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

The dosage and frequency for MTX/placebo and infliximab/placebo will depend on whether the patients reach remission as defined in the protocol (infliximab) and/or whether there are any side effects (MTX). Infliximab will be given by infusion and MTX intake will be oral.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Methotrexate, infliximab (Remicade®)

Primary outcome(s)
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 two consecutive visits after month 3 during the first 54 weeks.

Key secondary outcome(s))
Comparison, Group I versus Group II and Group III of:
1. The presence of persistent clinical remission at week 106
2. The presence of persistent clinical remission at week 54 since start of therapy
3. The presence of persistent clinical remission at week 106
4. Radiographic progression at week 22, 54 and 106
5. The presence of clinical remission at every time point during the trial
6. The presence of clinical remission by Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) at every time point during the trial
7. The presence of remission by Pinals criteria at every time point during the trial
8. The presence of near-remission (28-item Disease Activity Score [DAS28] less than 2.6) at every time point during the trial
9. The duration of clinical remission or near-clinical remission during the entire trial
10. Time to remission
11. Time to relapse after withdrawal of infliximab therapy in patients who achieved persistent clinical remission
12. All variables included in the World Health Organization/International League of Associations for Rheumatology (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], C-Reactive Protein [CRP], Erythrocyte Sedimentation Rate [ESR]) at every time point during the trial
13. DAS28, SDAI, CDAI and Rheumatoid Arthritis Disease Activity Index (RADAI) at every time point during the trial
14. American College of Rheumatology (ACR) 50 and 70 response, 36-item Short Form health survey (SF36), fatigue (Visual Analogue Scale [VAS]) and pharmacoeconomics at week 2, 6, 14, 22, 30, 38, 54, 70 and 106
15. Glucocorticoid and Non-Steroidal Anti-Inflammatory Drug (NSAID)/Cyclooxygenase (COX)-2 selective inhibitors (Coxib) dosage at every time point during the trial
16. Number of visits at which relapse from remission was noted

Completion date
07/10/2013

Eligibility

Key inclusion criteria
All patients to be included into this trial must meet the following inclusion criteria:
1. Men and women, between 18 and 75 years of age, capable of understanding and signing an informed consent
2. The presence of arthritis:
2.1. Must be established in a rheumatology centre
2.2. Must be present in at least two joints of the 66 joint count, of which at least one joint must be an Metacarpophalangeal- (MCP-), or a Proximal Interphalangeal- (PIP-) (Interphalangeal- [IP-]), or a wrist- or a Metatarsophalangeal- (MTP-) joint. Two MTP-joints will not suffice. Any kind of polyarthritis (= 6 joints of any kind) will be sufficient
2.3. Without any previous episodes of inflammatory joint disease
3. Duration of symptoms:
3.1. Must be reported by the subject and should involve the inflamed joints described under point 2
3.2. Must be 2 weeks at least
3.3. Must be 16 weeks at most, as reported by the subject, including the observation period of at least 2 weeks by the physician
4. Confirmation of persistent arthritis:
4.1. Duration must be 2 weeks at least
4.2. Duration must be 12 weeks at most
4.3. Must be documented by the same rheumatology centre that established arthritis at the first visit
4.4. Must involve at least one of the same joints as were involved at the first visit
5. Men and women of childbearing potential must use adequate birth control measures (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, implantable or injectable contraceptives or surgical sterilisation) for the duration of the study and should continue such precautions for 6 months after receiving the last medication
6. Are considered eligible according to the Tuberculosis (TB) eligibility assessment, screening, and early detection of reactivation rules (defined in the protocol)
7. Chest radiograph (which must not be older than three months at the visit 1/day 0 visit) must show no evidence of malignancy, infection, or fibrosis. The chest radiograph should also show no atypical scarring, cavitary lesions, or calcified granulomas, as evidence of past tuberculosis infections, without a documented history of adequate therapy

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Key exclusion criteria
Patients must not:
1. Have arthritis with a distinct diagnosis, made after a routine diagnostic work-up (examples are Systemic Lupus Erythematosus [SLE], psoriatic arthritis, systemic sclerosis, gout, pseudogout, Lyme arthritis, reactive arthritis, Parvo viral arthritis)
2. Be incapacitated, largely or wholly bedridden, or confined to a wheelchair, or have little or no ability for self care
3. Weigh more than 100 kg
4. Use glucocorticoids greater than 10 mg/day prednisone or equivalent
5. Have received intramuscular or intra-articular injection of steroids in the previous month
6. Have screening laboratory test results as follows:
6.1. White Blood Cells (WBCs) less than 3.0 x 10^9 cells/L
6.2. Platelets less than 100 x 10^9 cells/L
6.3. Serum creatinine greater than 1.4 mg/dL
6.4. Serum transaminase levels exceeding 2 times the upper limit of normal for the site laboratory
7. Have had any previous treatment with monoclonal antibodies or antibody fragments
8. Have a history of receiving human/murine recombinant products or a known allergy to murine products. A known allergy to murine product is definitely an exclusion criterion
9. Have had prior treatment with MTX and/or other Disease Modifying Anti-Rheumatic Drugs (DMARDs) (except hydroxychloroquine)
10. Have documentation of seropositivity for Human Immunodeficiency Virus (HIV)
11. Have documentation of a positive test for hepatitis B surface antigen or hepatitis C-antibodies
12. Have a history of alcohol or substance abuse within the preceding 6 months that, in the opinion of the investigator, may increase the risks associated with study participation or study agent administration, or may interfere with interpretation of results
13. Have a known history of serious infections (such as, but not limited to hepatitis, pneumonia, or pyelonephritis) in the previous 3 months
14. Have a known history of a demyelinating disease, such as multiple sclerosis
15. Have or have had an opportunistic infection (e.g., herpes zoster [shingles], cytomegalovirus, Pneumocystis carinii, aspergillosis, histoplasmosis, or mycobacteria other than TB) within 12 months prior to screening
16. Have undergone any joint replacement surgery
17. Have a chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (e.g., bronchiectasis), sinusitis, recurrent urinary tract infection, open, draining or infected skin wound or ulcer
18. Be considered ineligible according to the TB eligibility assessment, screening, and early detection of reactivation rules (defined in the protocol)
19. Have a chest radiograph at screening that shows evidence of malignancy, infection, or any abnormalities suggestive of TB
20. Have a history of lymphoproliferative disease, including lymphoma or signs suggestive of possible lymphoproliferative disease such as lymphadenopathy of unusual size or location (e.g., nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or periaortic area), or splenomegaly

21. Currently have any known malignancy other than the condition being treated or have a history of malignancy within the previous 5 years, with the exception of basal cell or squamous cell carcinoma of the skin that has been fully excised with no evidence of recurrence
22. Have current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, haematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease
23. Be unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access
24. Use any investigational drug within 3 months prior to screening or within five half-lives of the investigational agent, whichever is longer
25. Have presence of a transplanted solid organ (with the exception of a corneal transplant greater than 3 months prior to screening)
26. Have a concomitant diagnosis or history of congestive heart failure (New York Heart Association [NYHA] class III or IV)
27. Be women who are pregnant, nursing, or planning pregnancy within 6 months after the last infusion

Date of first enrolment
04/10/2007

Date of final enrolment
14/02/2012

Locations

Countries of recruitment
Austria

Germany

Greece

Italy

Netherlands

Spain

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Sponsor information

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ROR
https://ror.org/05n3x4p02

Funder(s)

Funder type
Industry

Funder Name
Janssen

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	09/08/2018		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes