A Double Blind, Randomized, Placebo Controlled, Multi-Center Trial of Anti-TNF¨¢ Chimeric Monoclonal Antibody (Infliximab, Remicade®) in Combination with Methotrexate in Patients with Very Early Inflammatory Arthritis.

No registrations found.

Ethical review	Not applicable
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON28713

Source
NTR

Brief title
DINORA

Health condition

Very early inflammatory arthritis.

Sponsors and support

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Source(s) of monetary or material Support: Self-financing research.

Intervention

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:

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 SDAI and 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 (DAS28 < 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 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;

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

14. ACR 50 and 70 response, SF36, Fatigue (VAS) and Pharmacoeconomics at week 2, 6, 14, 22, 30, 38, 54, 70 and 106;

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

16. 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

N/A

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).

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Eligibility criteria

Inclusion criteria

1. Men and women, >= 18 and <= 75 years of age, capable of understanding and signing an informed consent;

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, of which at least one joint must be an MCP-, or a PIP- (IP-) or a wrist- or a MTP-joint. Two MTP-joints will not
suffice. Any kind of polyarthritis (>= 6 joints of any kind) will be sufficient;

c. Without any previous episodes of inflammatory joint disease;

3. Duration of symptoms :

a. Must be reported by the subject and should involve the inflamed joints described under 2;

b. Must be 2 weeks at least, according to the algorithm in Table 1 (subjects will not receive study treatment before 12 weeks of symptom duration according to the algorithm in Table 1);

c. Must be 16 weeks at most, as reported by the subject, including the observation period of at least 2 weeks by the physician, according to the algorithm in Table 1;

4. Confirmation of persistent arthritis:

a. Duration must be 2 weeks at least, according to the algorithm in Table 1.

b. Duration must be 12 weeks at most, according to the algorithm in Table 1.

c. Must be documented by the same rheumatology center that established arthritis at the first visit;

d. 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 sterilization) 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 Section 7.14: Tuberculosis Eligibility Assessment, Screening, and Early Detection of Reactivation;

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.

Exclusion criteria

1. Have arthritis with a distinct diagnosis, made after a routine diagnostic work-up (examples are 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 > 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:

a. White blood cells (WBCs) < 3.0 x 109 cells/L;

b. Platelets < 100 X 109 cells/L;

c. Serum creatinine > 1.4 mg/dL;

d. 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 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 Cantibodies;

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 (eg, 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 (eg. 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 Section on: Tuberculosis Eligibility Assessment, Screening, and Early Detection of Reactivation Rules;

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 (eg, 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, hematologic, 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 5 half-lives of the investigational agent, whichever is longer;

25. Have presence of a transplanted solid organ (with the exception of a corneal transplant > 3 months prior to screening).

26. Have a concomitant diagnosis or history of congestive heart failure (NYHA class III or IV);

27. Be women who are pregnant, nursing, or planning pregnancy within 6 months after the last infusion.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-10-2007
Enrollment:	200
Type:	Anticipated

Ethics review

Not applicable

Application type:	Not applicable

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
NTR-new	NL1045
NTR-old	NTR1078
Other	: DINORA4
ISRCTN	ISRCTN21272423

Study results

Summary results
N/A