ISRCTN49682259 https://doi.org/10.1186/ISRCTN49682259

Remission Induction in Very Early Rheumatoid Arthritis: a comparison of etanercept plus methotrexate plus steroid with standard therapy

Submission date 28/09/2007	**Recruitment status** Stopped	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 28/09/2007	**Overall study status** Stopped	
Last Edited 01/12/2015	**Condition category** Musculoskeletal Diseases	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Dr P Jobanputra

Contact details
Rheumatology
Selly Oak Hospital
Birmingham
United Kingdom
B29 6JD

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N0265183512

Study information

Scientific Title
Remission Induction in Very Early Rheumatoid Arthritis: a comparison of etanercept plus methotrexate plus steroid with standard therapy

Study objectives
1. Rheumatoid arthritis (RA) is a debilitating chronic inflammatory disease which affects 1% of the European population. RA is associated with significant joint damage, disability and an enhanced mortality. Current treatment strategies target patients once joint inflammation has been present for several months and it is clear that the patient has developed a disease that is going to persist in the long term. After the first 3 months of symptoms the persistence of chronic inflammation in the rheumatoid joint is maintained by an expansion of fibroblast cells in the joint lining which drives the accumulation of inflammatory white cells in the joint. Treating RA at this stage reduces the amount of inflammation present in the joint but cannot cure RA. We have recently identified that the very early phase of arthritis (within the first 12 weeks of symptoms) represents a unique phase in the development of RA. During this time, before the fibroblast layer has expanded, the processes operating to cause pain and swelling in the joint are dependent on inflammatory cells such as lymphocytes.
Building on these observations, we propose to test the hypothesis that the disease processes in the very early stages of RA are fundamentally different to those in established chronic disease. This will be done by assessing whether treatment of patients at very high risk of the subsequent development of RA during this very early phase, with a short course of potent immunosuppression, can permanently switch off inflammation and prevent the development of RA.
2. The utility of synovial and peripheral blood cytokine profiles and gene expression profiles in predicting response to therapy in patients with very early inflammatory arthritis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomized single-blind pilot study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Musculoskeletal Diseases: Rheumatoid arthritis (RA)

Interventions
We propose a pilot study to assess whether the first 12 weeks after the onset of symptoms represents a therapeutic window in patients at high risk of the subsequent development of RA by determining whether aggressive therapy during this phase will induce disease remission that can be maintained without the ongoing use of DMARDs.

We propose an intervention study in which patients with synovitis of less than 12 weeks duration who have a very high probability of developing RA (anti-CCP Ab+ve and RF+ve) are randomized to receive either to:
1. Conventional therapy: parenteral steroid (with the option of adding methotrexate after 3 months of symptoms) or
2. Parenteral steroid plus methotrexate plus etanercept.

This study will allow us to assess whether very early aggressive therapy, which includes the antagonism of TNF-alpha with etanercept, can induce disease remission when administered during the biologically distinct phase that characterises the first 12 weeks after symptom onset. The rationale for the choice of etanercept plus
methotrexate plus parenteral depomedrone as the drug regimen to attempt to switch disease off is strong. TNF-alpha has pleiotropic effects driving the immune response and occupies a central position in the inflammatory cascade. Indeed, data from our group suggests that macrophages, a significant source of TNF-alpha, are important in maintaining the transient persistence that characterises very early RA.

PATIENT RECRUITMENT:
Recruitment to this study will be through the successful rapid access Very Early Arthritis Clinic which Dr Karim Raza has run at City Hospital since 2000. This clinic has provided the patient population for our group's work addressing pathogenic mechanisms in early inflammatory arthritis. Recruitment will be enhanced by collaboration with Rheumatologists within the West Midlands including at Selly Oak Hospital, University Hospital Birmingham NHS Foundation Trust, Sandwell Hospital, Sandwell and West Birmingham Hospitals NHS Trust and Royal Wolverhampton Hospitals NHS Trust. We estimate that recruitment of 20 patients needed in this study will take 12 months.

RANDOMIZATION:
Will be coordinated through the Birmingham Clinical Trials Unit. Patients will be randomised 1:1 to treatment with either 1. Parenteral steroid (with the option of adding methotrexate after 12 weeks of symptoms) or 2. Parenteral steroid plus methotrexate plus etanercept.

BIOLOGICAL PREDICTORS OF THE RESPONSE TO TREATMENT: Serum, urine, peripheral blood mononuclear cells (PBMC), synovial fluid and, where possible, synovial tissue will be collected at clinical presentation. The response to therapy will be assessed in relation to baseline serum and synovial fluid cytokine profiles, urinary steroid profiles and lymphocyte, macrophage and fibroblast gene expression profiles.

TREATMENT:
BASELINE

Group 1: 120mg depomedrone (either intra-articular or intramuscular at the discretion of the treating Rheumatologist).
Group 2: 120mg depomedrone (either intra-articular or intramuscular at the discretion of the treating Rheumatologist) plus methotrexate (commenced at 7.5 mg per week and increased at 2 weekly intervals to 15 mg weekly or maximum tolerated dose) and folic acid (5 mg 6 days per week except day of methotrexate) plus etanercept (50mg one weekly subcutaneously)

WEEKS 0-12
Group 1: Methotrexate can be started at the discretion of the principal investigator at each site once the patient has had a symptom duration of >12 weeks i.e. if patient was recruited with a symptom duration of 11 weeks methotrexate could be commenced at week 2 and if patient was recruited with a symptom duration of 6 weeks methotrexate could be commenced at week 7 etc.
Group 2: Further 120mg depomedrone at weeks 4 and 8.

WEEKS 12-24
Groups 1 and 2: The methotrexate dose can be increased to 25 mg per week if synovitis remains active. Further 120 mg of parenteral depomedrone (intra-articular or intramuscular) will be permitted as clinically required though not after week 18. These decisions will be at the discretion of the principal investigator at each site. In patients intolerant of methotrexate, the use of sulfasalazine (500mg once daily increasing by 500mg per week to 1g twice daily) will be permitted in group 1.

WEEK 24
Patients in clinical remission (DAS28 <2.6 plus no joint swelling) will have all therapy withdrawn. The assessing blinded metrologists will inform the rheumatologist who has recruited the patient to the trial at each site whether the patient meets criteria for withdrawal of therapy.

WEEK 24-48
All patients will be assessed every 4 weeks by the local recruiting rheumatologist and at weeks 36 and 48 by the blinded metrologist.
For patients who were in clinical remission at week 24 and in whom therapy was withdrawn, therapy will be recommenced with methotrexate at the dose previously effective in controlling synovitis if disease activity recurs (DAS28 >2.6 and / or joint swelling as assessed by the blinded metrologists). This will be supplemented with up to 120 mg of parenteral depomedrone (intra-articular or intramuscular) between weeks 24 and 30 and between weeks 36 and 42 as clinically required. Patients will be asked to contact the rheumatology team between assessments if they believe disease activity has recurred at which point they will be assessed by the blinded metrologists to determine whether they meet criteria for the reintroduction of methotrexate therapy.
For patients not in clinical remission at week 24 therapy DMARD therapy will be continued but etanercept will be stopped. These patients will be assessed every 4 weeks by the local investigator and at weeks 36 and 48 by the blinded metrologist. Further therapy with up to 120 mg of parenteral depomedrone (intra-articular or intramuscular) will be permitted as clinically required between weeks 24 and 36 and week 36 and 42.
In addition, the use of sulfasalazine (500mg once daily increasing by 500mg per week to 1g twice daily) and hydroxychloroquine (up to 6.5mg/kg/day) will be permitted in both groups at the discretion of the local co-investigator.

WEEK 48
Subsequent therapy will be used at the discretion of the treating Rheumatologist according to conventional practice.

ASSESSMENTS:
The assessing metrologists and radiologist will be blinded to treatment group. Patients will be assessed at baseline and at weeks 12, 24, 36, 48 and 96 by the blinded metrologists and for the collection of biological samples. Other assessment and management of the patient will be carried out by the rheumatologist who recruited the patient to the trial (the local co-investigator).

SCREENING (WEEK -1)
Joint counts (ACR 68 joint tender joint count and 66 joint swollen joint count), RF, anti-CCP Ab, FBC, U&E, Creatinine, LFT.

BASELINE (WEEK 0)
Clinical assessments: Joint counts, patient assessments of pain and global assessment of disease activity (10cm VAS), physician global assessment of disease activity (10cm VAS), patient assessment of physical function (HAQ) and health status (EuroQuol-5D).Laboratory assessments: CRP and ESR. Radiological assessments: Chest radiograph, Plain radiographs of hands and feet, gadolinium enhanced MRI of hands and wrists and ultrasound examination of hands and wrists. Biological material for research studies: Serum will be collected for analysis of soluble mediators of inflammation. A 24 hour collection of urine will be taken to assess the function of the hypothalamic- pituitary-adrenal axis. PBMCs will be collected for micro array analysis of gene expression and HLA typing. Synovial fluid will be aspirated; the cellular component will be analysed for gene expression and leukocyte function and the acellular portion will be analysed for soluble mediators of inflammation. Where possible, synovial tissue will be collected by arthroscopic biopsy. Cytokines will be measured in synovial fluid and serum using the luminex system which we have adapted for the assessment of biological fluids from patients with RA 12. Synovial cell populations will be purified and gene expression studied by Affymetrix microarray. In addition, we will use microfluidics RT PCR to study specific cytokines. These studies have been funded independently by an independent project grant from Wyeth.

Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48:
Monthly clinical assessment at centre from which patient was recruited and measurement of CRP, ESR, FBC, U&E, Creatinine, LFT at the time points above and also at week 96.

Weeks 12, 24, 36, 48 and 96:
Assessments by blinded metrologist for joint counts, patient assessments of pain and global assessment of disease activity (10cm VAS), physician global assessment of disease activity (10cm VAS), patient assessment of physical function (HAQ) and health status (EuroQuol-5D). Collection of blood for gene expression profiling in leukocytes and the measurement of cytokines in serum and the collection of 24 hour urine samples for measurement of steroid hormone levels.

Weeks 24, 48 and 96:
Gadolinium enhanced MRI of hands and wrists and ultrasound examination of hands and wrists at weeks 24, 48. Plain radiographs of hands and wrists will be performed at weeks 48 and 96.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)

Etanercept, methotrexate

Primary outcome measure
1. The primary endpoint will be the percentage of patients in drug free clinical remission at week 48 having withdrawn therapy at week 24 i.e. the induction of drug free remission.
2. Clinical remission will be defined as a DAS28 score of <2.6 (EULAR definition of remission) plus no clinical evidence of joint swelling.

Secondary outcome measures
1. The percentage of patients in clinical remission (DAS28 score of <2.6 plus no clinical evidence of joint swelling) at week 24 (when all drugs will be withdrawn if remission has been achieved).
2. The percentage of patients in clinical remission defined according to ARA criteria at week 24 (when all drugs will be
withdrawn if remission has been achieved).
3. The percentage of patients in radiological remission at week 24 (no MRI or ultrasound evidence of synovitis in hands and wrists).
4. Clinical disease activity measures, including ACR responder rates (20%, 50%, and 70%), Disease Activity Score in 28 joints (DAS28), functional assessments (HAQ) and health status (EuroQuol-5D) at week 24.
5. The percentage of patients in drug free clinical remission defined according to ARA criteria at week 48 having withdrawn therapy at week 24.
6. The percentage of patients in drug free radiological remission (no MRI or ultrasound evidence of synovitis) at week 48 having withdrawn therapy at week 24.
7. Clinical disease activity measures, including ACR responder rates (20%, 50%, and 70%), Disease Activity Score in 28 joints (DAS28), functional assessments (HAQ) and health status (EuroQuol-5D) at week 48.
8. The rate of progression of radiological change on conventional radiographs scored according to the van der Heijde modification of the total Sharp score from baseline to week 48 and 96.
9. In addition we will assess biological predictors of response to therapy.

Overall study start date
13/12/2005

Completion date
30/05/2010

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
Patients with very early synovitis of less than 12 week duration will be identified via the rapid access early arthritis clinics run at the participating centres. Patients fulfilling clinical inclusion criteria and not meeting exclusion criteria will have measurements of their serum levels of rheumatoid factor and anti-CCP antibody and will be given an information sheet on the study. They will be asked to attend for follow up review after 2-7 days. Those patients who are seropositive for both rheumatoid factor and anti-CCP antibody will be invited to participate in the trial.
Inclusion criteria:
1. Age over 18 years

2. Synovial swelling of at least 1 joint confirmed by clinical assessment
3. Seropositivity for RF and anti-CCP Ab
4. Women of childbearing potential or men capable of fathering children must be using adequate birth control measures (eg abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, surgical sterilization) during the study
5. Female subjects of childbearing potential must test negative for pregnancy
6. Patients should be able to give informed consent to study entry

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
20

Key exclusion criteria
1. Duration of symptoms attributable to inflammatory joint disease (pain, swelling or early morning stiffness of >1 hour) of >12 weeks
2. Previous history of inflammatory arthritis
3. Previous use of DMARDs or anti-TNF-agents
4. Any current inflammatory condition with signs or symptoms that might confound the diagnosis (e.g. connective tissue disorders)
6. A history or other evidence of latent or active granulomatous infection, including TB, histoplasmosis or coccidioidomycosis, prior to study entry
7. Administration, or expected administration, of any live virus or bacterial vaccination within 3 months before the first administration of study agent or during the trial
8. A history of an infected joint prosthesis, or administration of antibiotics for a suspected infection of a joint prosthesis, if that
prosthesis has not been removed or replaced
9. Known infection with HIV, hepatitis B, or hepatitis C
10. A serious infection that in the opinion of the investigator precludes receipt of a TNF blocking agent
11. Serious and uncontrolled co-existing disease that in the opinion of the investigator preclude the use of TNF-blocking medication, methotrexate or depomedrone (including pulmonary disease on chest radiograph, heart failure, history of demyelinating disease such as multiple sclerosis or optic neuritis)
12. Bleeding disorder or the use of anti-coagulants
13. Any known malignancy or a history of malignancy within the previous 5 years (with the exception of a basal cell carcinoma that has been treated with no evidence of recurrence)
14. Any contraindication to etanercept, methotrexate or parenteral depomedrone

Date of first enrolment
12/10/2007

Date of final enrolment
30/05/2010

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Selly Oak Hospital
Birmingham
United Kingdom
B29 6JD

Sponsor information

Organisation
Record Provided by the NHSTCT Register - 2007 Update - Department of Health

Sponsor details
The Department of Health
Richmond House
79 Whitehall
London
United Kingdom
SW1A 2NL
+44 (0)20 7307 2622
dhmail@doh.gsi.org.uk

Sponsor type
Government

Website
http://www.dh.gov.uk/Home/fs/en

Funder(s)

Funder type
Government

Funder Name
University Hospital Birmingham NHS Trust (UK), NHS R&D Support Funding

Results and Publications

Publication and dissemination plan
Insufficient data available to publish

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available