ISRCTN15819795 https://doi.org/10.1186/ISRCTN15819795

Effect of anakinra (soluble interleukin-1 receptor antagonist) as combination therapy: second UK combination therapy in early rheumatoid arthritis

Submission date
15/12/2006

Recruitment status
No longer recruiting

Registration date
26/01/2007

Overall study status
Completed

Last Edited
05/05/2016

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol

Background and study aims
The conventional management of rheumatoid arthritis (RA) is based on combinations of simple painkillers (analgesics), non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs), with or without steroids. With such conventional therapy many RA patients have an aggressive course with progressive joint destruction and marked disability developing over 5-10 years. Although it is generally accepted that DMARDs help to slow the course of RA, when DMARDs are used one after another, many patients continue to deteriorate. Together these observations have led to a shift in the management of RA. Firstly, rheumatologists start DMARD therapy as early as possible. Secondly, there is increasing use of combinations of two or more DMARDs given at the same time. The emergence of new therapies for RA has led to renewed optimism in the ultimate ability to control the disease process. There is little doubt that the best management of RA will require combination DMARD therapy. This will need to be started within the first year of disease onset. At present it is not clear what will be the best combination therapy. With an increasing number of new biological agents available to patients, or at various stages of development, the combination of such agents with non-biological DMARDs such as methotrexate, sulphasalazine and gold, should be evaluated. The study will look at whether the addition of a daily injection of Anakinra to normal DMARD (Disease Modifying Anti Rheumatoid Drug) therapy will result in a reduction in the number and severity of joint erosions in patients who have been recently diagnosed with rheumatoid arthritis.
The study will also look at other aspects in the management of rheumatoid arthritis, such as control of the level of inflammation and quality of life and collect information on health economics. This will be done using standard validated questionnaires.

Who can participate?
159 patients (males and females aged over 18 years with early rheumatoid arthritis (disease duration of less than 12 months at study entry) in participating centres.

What does the study involve?
Participants receive either only Methotrexate, or Methotrexate with additional daily injections of Anakinra. Each participant will spend 12 months on treatment and then be monitored for a further 12 months. Participants will be assessed at the beginning of the study and 6, 12 and 18 months after this.

What are the possible benefits and risks of participating?
Patients with early rheumatoid arthritis benefit from taking methotrexate which reduces joint inflammation and pain and improves disability. Anakinra has similar benefits in active rheumatoid arthritis. In established disease the two drugs are more effective in combination that when given singly. Their combined impact in early arthritis is unknown. Like all disease modifying drugs methotrexate can cause minor side effects like rashes and can cause rare side effects like liver damage. We regularly monitor blood tests to minimize the risk of toxicity. Like all biologic treatments Anakinra can increase the risk of infections. It also often causes temporary injection site reactions.

Where is the study run from?
King's Musculoskeletal Clinical Trials Unit, Kings College London (UK)

When is the study starting and how long is it expected to run for?
October 2003 to January 2010

Who is funding the study?
Amgen Limited (UK)

Who is the main contact?
Prof. David Scott
d.scott1@nhs.net

Study website
http://www.kcl.ac.uk/medicine/research/divisions/diiid/centres/ctu/research/trials/cardera2/index.aspx

Contact information

Type(s)
Scientific

Contact name
Prof David Scott

Contact details
Academic Rheumatology
Weston Education Centre
King's College London
Denmark Hill
London
United Kingdom
SE5 9RJ

Additional identifiers

EudraCT/CTIS number
2004-001123-38

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Version 10 (23/08/2006)

Study information

Scientific Title
Effect of anakinra (soluble interleukin-1 receptor antagonist) as combination therapy: second UK combination therapy in early rheumatoid arthritis

Acronym
CARDERA2

Study objectives
This study will test the hypothesis that in patients with early Rheumatoid Arthritis (RA) methotrexate-anakinra therapy will reduce the progression of erosive disease. Specifically it will decrease the number of patients developing new erosions by 40% compared with methotrexate monotherapy alone over 12 months.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South East MREC, 25/10/2002, ref: MREC 02/01/89

Study design
Prospective randomised controlled multicentre trial

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
Rheumatoid arthritis

Interventions
1. Sequential monotherapy:
Patients will be given initially 7.5 mg/week methotrexate, increasing every two weeks by 2.5 mg to 15 mg/week.

2. Sequential monotherapy plus Anakinra:
Patients randomised to receive Anakinra with methotraxate-based sequential monotherapy, initially will be given 100 mg/day of Anakinra by subcutaneous injection and 7.5 mg/week methotrexate, increasing every two weeks by 2.5 mg to 15 mg/week. The dose of Anakinra is fixed and will not be escalated throughout the study.

For both trial arms the local hospital consultant may vary the rate that the methotrexate is increased and the final dose depending on the clinical situation. If there is persistent active disease, the dosage can be increased by the supervising rheumatologist to a maximum of 25 mg /week. If, in the opinion of the local hospital consultant, there are significant side effects to methotrexate or there is either no response or a very inadequate response, patients will discontinue methotrexate and take a second DMARD. This DMARD can be any of sulphasalazine, leflunomide, azathioprine, penicillamine, ciclophosphomide or gold.

If, in the opinion of the local hospital consultant, there are significant side effects to the second DMARD or there is either no response or a very inadequate response, patients will discontinue the second DMARD and take a third DMARD, which can be any of the DMARDS listed above. The order in which the DMARDS are prescribed is at the discretion of the supervising consultant.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Anakinra (soluble interleukin-1 receptor antagonist) and methotrexate

Primary outcome measure
The difference in the number and severity of joint erosions as measured with the van der Heijdi Modified Sharp score.

Secondary outcome measures
1. Increases in the combined van der Heijde Modified Sharp score and in its three individual components
2. Decreases in disease activity measured by modified Disease Activity Score (DAS) and American College of Rheumatology (ACR) response criteria
3. Changes in function measured by Health Assessment Questionnaire (HAQ)
4. Quality of life measured by Short Form health survey (SF-36) and EuroQol questionnaire
5. Health economics analysis measured by collection of standardised data set (used previously)

Overall study start date
01/10/2003

Completion date
01/01/2010

Eligibility

Key inclusion criteria
1. RA by the 1987 criteria of the American College of Rheumatology
2. Disease duration of less than 12 months
3. The clinical need for treatment with a Slow Acting Anti-Rheumatic Drug (SAARD) as shown by evidence of active RA with three out of the following four criteria:
3.1. At least three swollen joints on a 28 joint score
3.2. At least six tender joints on a 28 joint score
3.3. At least 45 minutes morning stiffness
3.4. Erythrocyte Sedimentation Rate (ESR) of at least 28 mm/h
4. Patients must be willing and able to give informed consent
5. Aged at least 18

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
158

Key exclusion criteria
1. Other forms of inflammatory arthritis (e.g. psoriatic arthritis, systemic lupus erythematosus)
2. Previous treatment with methotrexate
3. Contraindications or known intolerance to any of the drugs allowed on this trial (including Non Steroidal Anti-Inflammatory Drugs [NSAID], Steroids and Disease Modifying Anti-Rheumatic Drugs [DMARDs])
4. Other serious medical disorders (e.g. hepatic failure, gout, cardiac failure, tuberculosis, current malignant disease)
5. Any acute or chronic infection, including pneumonias
6. Females of child bearing and males of child fathering potential who are not taking adequate contraceptive protection
7. Neutrophil count less than 1.5 x 10^12/dl or platelet count less than 100 x 10^12/dl
8. Abnormal liver function test (gamma-Glutamyl Transferase [gGT] more than three times or Aspartate aminotransferase [AST]/Alanine aminotransferase [ALT] more than two times upper limit of normal)

9. Abnormal chest x-ray results
10. Patients with severe renal impairment (creatinine clearance less than 30 ml/min). Patients with a creatinine clearance between 30 and 50 ml/min can be entered into the trial but must be closely monitored
11. Patients taking low-dosage oral steroids for the treatment of RA. Patients taking a short-course of oral steroids for another condition may be included providing the daily dosage of steroids is less than 20 mg total

Date of first enrolment
01/10/2003

Date of final enrolment
01/01/2010

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
King's College London
London
United Kingdom
SE5 9RJ

Sponsor information

Organisation
King's College London (UK)

Sponsor details
Strand
London
England
United Kingdom
WC2R 2LS

Sponsor type
University/education

Website
http://www.kcl.ac.uk

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Industry

Funder Name
Amgen (International)

Alternative Name(s)
Amgen Inc., Applied Molecular Genetics Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

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	01/01/2016		Yes	No