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A placebo controlled study of the effect of EXTended treatment with Rituximab on resistant Rheumatoid Arthritis: Clinical and radiological outcomes

Submission date
02/01/2008

Recruitment status
No longer recruiting

Registration date
27/03/2008

Overall study status
Completed

Last Edited
29/06/2016

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

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
RR06/7719

Study information

Scientific Title
A placebo controlled study of the effect of EXTended treatment with Rituximab on resistant Rheumatoid Arthritis: Clinical and radiological outcomes

Acronym
EXTRRA

Study objectives
Extending the standard dosing regimen of rituximab (3 doses rather than 2), will lead to better clinical outcomes in patients as measured by radiographic changes, B cell depletion and patient report.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved by the West Glasgow Research Ethics Committee on 4 September 2007 (ref: 07/S0703 /68)

Study design
Single-centre study consisting of parts:
Part 1: Open-label study. Part 2: Double-blind, partially randomised, placebo-controlled study.

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

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

Part 1 open-label study (first two doses of IMP):
2 doses x 1 g rituximab infusion (with methylpred pre-infusion) plus methotrexate as standard treatment dictates.

Part 2 double-blind, placebo-controlled study (third dose: IMP or placebo):
After the second rituximab infusion in Part 1 open-label study, the level of B-cell remaining in each patient will be measured. Those who have none remaining will be automatically assigned to the placebo arm. Those who still have remaining B-cells (non-depletors) will be randomly assigned to either placebo or 1 g rituximab. The clinicians will be blind to this information. Both IMP and placebo groups will receive methotrexate as standard treatment dictates, but no methylpred pre-infusion will be given.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Rituximab

Primary outcome measure
Proportion of patients with B cells receiving three doses of rituximab vs proportion of patients with B cells who receive standard dose (two doses) rituximab who achieve ACR20 response at Week 28.

Secondary outcome measures
Disease Activity Measures:
1. Proportion of patients with ACR50 response at 6 months
2. Proportion of patients with ACR70 response at 6 months
3. Change in DAS28-ESR from baseline to 6 months
4. EUropean League Against Rheumatism (EULAR) response rates at 6 months
5. Change in ACR core set from baseline to 6 months
6. Change in 36-item Short Form health survey (SF-36) from baseline to 6 months
7. Proportion of patients achieving DAS28-ESR remission at 6 months
8. Proportion of patients achieving DAS28-ESR low disease state at 6 months

Disability measures:
1. Change in Health Assessment Questionnaire (HAQ) score from baseline at weeks 12, 28, 40 and 52

Quality of Life:
1. Change in the Rheumatoid Arthritis Quality of Life (RA-QoL) score from baseline at weeks 12, 28, 40 and 52

Radiological:
1. Change in modified Sharp Radiographic Score for X-rays of dominant hand from baseline at 12 months, measuring total score, erosion score and joint space narrowing score
2. Change in ultrasound score for synovitis in dominant hand, assessed on grey scale and power

Doppler, from baseline at weeks 28, 40 and 52
3. Change in MRI score (high field and peripheral) for synovitis, bone oedema and erosions in dominant hand from baseline at weeks 12, 28, and 40

Immunological:
1. Proportion of patients with PPC depletion (measured at week 2, 4 and 6) and correlation of this with response and relapse (measured at 6, 9 and 12 months)
2. Change in serological status (rheumatoid factor positivity or not) from baseline at 6 months

Overall study start date
04/09/2007

Completion date
04/09/2010

Eligibility

Key inclusion criteria
1. Able and willing to give written informed consent and comply with the requirements of the study protocol
2. Patients with rheumatoid arthritis for at least 6 months, diagnosed according to the revised 1987 American College of Rheumatology (ACR) criteria for the classification of rheumatoid arthritis
3. Patients who have experienced an inadequate response to previous or current treatment with etanercept, infliximab or adalimumab because of toxicity or inadequate efficiency (etanercept for >3 months at 25 mg twice weekly, at least 4 infusions of infliximab at >=3 mg/kg or adalimumab for >=3 months at 40 mg every other week) or be unsuitable for treatment with anti-TNF therapy because of contra-indication
4. Patients who have been washed out from etanercept, infliximab or adalimumab or ¡Ý4 weeks prior to treatment with rituximab
5. All Disease Modifying Anti-Rheumatic Drugs (DMARDs) other than methotrexate should be withdrawn at least 4 weeks prior to rituximab therapy (see above for anti-TNF therapy)
6. 28-item Disease Activity Score (DAS28) >3.2
7. Age 18-80 years
8. Corticosteroids (<=10 mg/day prednisolone or equivalent) permitted if stable for at least 4 weeks prior to screening and NSAIDs permitted if stable for at least 2 weeks prior to screening.
9. Patients of reproductive potential (males and females) using a reliable means of contraception (e.g., contraceptive pill, IntraUterine Device [IUD], physical barrier)
10. If female and of childbearing potential, a negative urine pregnancy test within two weeks prior to therapy
11. Presence of erosive joint disease of at least 1 joint on x-ray (except if Distal InterPhalangeal [DIP] joint of the hand)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
Both

Target number of participants
60

Key exclusion criteria
1. Bone/joint surgery within 8 weeks prior to therapy or joint surgery planned within 24 weeks of therapy
2. Rheumatic autoimmune disease other than RA or significant systemic involvement secondary to RA
3. History of, or current, inflammatory joint disease other than RA or other systemic rheumatic disorder

Excluded previous/concomitant medications:
1. Concurrent treatment with any DMARD (apart from methotrexate) or any anti-TNF therapy or other biologic agent
2. Treatment with any investigational agent within 4 weeks of screening or 5 half lives of the investigational drug
3. Previous treatment with any cell depleting therapy therapies including investigational agents (e.g., CAMPATH®, anti-CD4, anti-CD5, anti-CD3, antiCD19)
4. Intra-articular or parenteral steroids within 4 weeks prior to therapy except for joints undergoing arthroscopy and/or Magnetic Resonance Imaging (MRI) where IA steroids are not permitted within 12 weeks prior to therapy
5. Receipt of a live vaccine within 4 weeks prior to randomisation

Exclusions for General Safety:
1. History of severe allergic or anaphylactic reactions to humanised or murine monoclonal antibodies (e.g., infliximab or adalimumab)
2. Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine or gastrointestinal disorders
3. Known active bacterial, viral, fungal mycobacterial infection (including tuberculosis, or atypical mycobacterial disease but excluding fungal infection of the nailbeds) or any episode of infection requiring hospitalisation or treatment with intravenous (iv) antibiotics within 4 weeks of therapy or oral antibiotics within 2 weeks of therapy
4. History of, or currently active, primary or secondary immunodeficiency
5. History of solid organ malignancy in the past 5 years (excluding basal cell or squamous cell carcinomas of the skin which have been excised and cured)
6. Pregnant women or breastfeeding mothers
7. History of alcohol, drug or chemical abuse within 6 months prior to screening
8. Neuropathies or neurovasculopathies which might interfere with pain evaluation
9. Intolerance or contraindications to oral (po) or iv steroids

Laboratory exclusion criteria (at screening):
1. Serum creatinine >140 mmol/l
2. ASpartate aminoTransferase (AST) or ALanine aminoTransferase (ALT) >2.5 times upper limit of normal

3. Platelet count <100
4. Haemoglobin <8.5
5. Neutrophils <1.5x10.3/µl
6. Positive tests for hepatitis B surface antigen or hepatitis C antibody
7. Levels of IgG and/or IgM below 5.65 and 0.55 mg/mL respectively

Date of first enrolment
04/09/2007

Date of final enrolment
04/09/2010

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Chapel Allerton Hospital
Leeds
United Kingdom
LS7 4SA

Sponsor information

Organisation
University of Leeds (UK)

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Sponsor type
University/education

Website

http://www.leedsth.nhs.uk/sites/research_and_development

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Industry

Funder Name
Roche Pharmaceuticals (Switzerland)

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:	01/06/2015		Yes	No