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Efficacy of tocilizumab in patients with rheumatoid arthritis

Submission date	Recruitment status	[ ] Prospectively registered
29/04/2010	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
29/04/2010	Completed	[X] Results
Last Edited	**Condition category**	[ ] Individual participant data
20/05/2019	Musculoskeletal Diseases	

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)
2008-003011-12

Protocol serial number
7538

Study information

Scientific Title
Prospective randomised study assessing the efficacy of Tocilizumab with synovial analysis in patients with rheumatoid arthritis

Acronym
TOCRA

Study objectives
Aim:
To study the mode of action of tocilizumab in patients with active rheumatoid arthritis (RA) who have failed to respond to at least one tumour necrotising factor (TNF) antagonist, or are not candidates for such treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Leeds West Research Ethics Committee (REC) approved on the 27th February 2009 (ref: 08 /H1307/119)

Study design
Randomised interventional treatment trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Musculoskeletal; Subtopic: Musculoskeletal (all Subtopics); Disease: Musculoskeletal

Interventions
1. Tocilizumab intravenous (IV), 4-weekly for 48 weeks
2. Placebo IV, 4-weekly for 12 weeks

Then all patient receive tocilizumab/methotrexate, 2.5 mg or 10 mg tablets/7.5 - 10 mg syringe. Weekly dose up to 25 mg.

Total duration of treatment and follow-up: 56 weeks

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Tocilizumab, methotrexate

Primary outcome(s)
Changes in synovial tissue to identify onset and mechanism of action

Key secondary outcome(s))

1. To evaluate the safety of tocilizumab and methotrexate combination for the treatment of rheumatoid arthritis by assessment of:
1.1. Incidence, frequency of adverse events
1.2. Vital signs
1.3. Blood haematology, chemistry, urinalysis
1.4. Electrocardiogram (ECG)
2. To evaluate efficacy of tocilizumab and methotrexate combination by:
2.1. Clinical assessment:
2.1.1. Composite scores: ACR and DAS28/EULAR response
2.1.2. Patient pain visual analogue scale (VAS) and general health VAS
2.1.3. Duration of morning stiffness
2.1.4. Health Assessment Questionnaire (HAQ) and RAQol
2.1.5. Physician Global VAS
2.1.6. High sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR)
2.2. Radiological assessment:
2.2.1. MRI features (bone oedema and erosion score) in addition to synovial volume (primary outcome)
2.2.2. Ultrasonographical features (grey scale, power doppler and erosions)
2.2.3. Plain radiography
2.2.4. Bone densitometry
2.3. Synovial assessment:
2.3.1. Macroscopic synovitis and vascularity scores
2.3.2. Histological score and pro-inflammatory cytokine expression in biopsies
3. To evaluate predictive and mechanistic features of tocilizumab and methotrexate/disease-modifying anti-rheumatic drug (DMARD) combination by:
3.1. Biomarker, cell biology and genetics studies:
3.1.1. Predictive markers of response to tocilizumab
3.1.2. Mechanistic studies
3.1.3. Genetic studies to evaluate mechanism and response to tocilizumab

Completion date
01/11/2009

Eligibility

Key inclusion criteria
Subjects meeting all of the following criteria will be considered for enrolment into the study:
1. Male and female patients aged between 18 and 80 years
2. Diagnosis of rheumatoid arthritis (1987 revised American College of Rheumatology [ACR] criteria) confirmed at least 6 months prior to screening
3. Persistent RA disease activity with inadequate response whilst being treated with an anti-TNF agent for at least 12 weeks, or patients who have previously discontinued anti-TNF due to toxicity, or patients have previously qualified for anti-TNF (NICE/BSR criteria) but therapy is contra-indicated
4. Methotrexate dose stable for 12 weeks prior to screening and to be continued for the duration of the study
5. Subjects with active RA at baseline are defined as: Disease Activity Scale (DAS28) greater than 5.1
6. Patients on non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids must have remained on an unchanged regimen for at least 28 days prior to study drug administration
7. Patients must be able and willing to comply with the terms of this protocol including

attending for arthroscopy and imaging assessments
8. Informed consent must be obtained in writing for all subjects at enrolment into the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Not Specified

Sex
All

Total final enrolment
15

Key exclusion criteria
Subjects presenting with any of the following will not be included in the study:
1. Patients unwilling or unable to receive methotrexate for the duration of the study
2. Patients with inflammatory joint disease of different origin, mixed connective tissue disease, Reiter's syndrome, psoriatic arthritis, systemic lupus erythematosus, or any arthritis with onset prior to 16 years of age
3. Suspicion of diagnosis of tuberculosis (positive tuberculosis test (greater than 5 mm induration if previous BCG or greater than 10 mm if no previous BCG) or abnormal chest x-ray)
4. Patients with concomitant medical condition which would in the investigator's opinion compromise the patient's ability to tolerate, absorb, metabolise or excrete the study medication
5. Patients with serious infections within 3 month of enrolment (screening) or persistent infections
6. Patients at significant risk of infection (e.g. leg ulceration, indwelling urinary catheter, septic joint within 1 year [or ever if prosthetic joint still in situ])
7. Patients with malignancy (other than excised basal cell carcinoma) within the last 5 years before study entry (screening)
8. Patients with history of Felty's syndrome, uncontrolled diabetes, uncontrolled hypertension, unstable ischaemic heart disease, active bowel disease, active peptic ulcer disease, recent stroke (within three month before study entry screening), or other condition which, in the opinion of the investigator, would put the patient at risk to participate in the study
9. Known positive serology for hepatitis B or C, or human immunodeficiency virus (HIV)
10. Discontinuation of a prohibited disease-modifying anti-rheumatic drug (DMARD) (e.g. oral or injectable gold, chloroquine, hydroxychloroquine, cyclosporine, azathioprine, leflunomide, sulphasalazine) or TNF-blocker (infliximab, etanercept or adalimumab) must occur at least 28 days prior to study drug administration (week 0)
11. Patients with acute major trauma
12. Patients with body weight less than 45 kg
13. Clinically relevant cardiovascular, hepatic, neurologic (such as multiple sclerosis, optic neuritis etc.), endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult
14. Impaired hepatic function, as shown by:
14.1. Alanine aminotransferase (ALT) or alkaline phosphatase (ALP) greater than or equal to 2 times the laboratory upper limit of normal

14.2. Serum albumin less than 30 g/l
15. Patients with significantly impaired bone marrow function as for example significant anaemia, leukopenia, neutropenia or thrombocytopenia as shown by the following laboratory values:
15.1. Haemoglobin less than 8.5 g/dl
15.2. Haematocrit less than 30%
15.3. Platelet count less than 100 x 10^9/L
15.4. White blood cell count less than 3.5 x 10^9/L
15.5. Neutrophils count less than 1 x 10^9/L
16. Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome or impaired renal function, as shown by:
16.1. Serum creatinine greater than 150 umol/L
16.2. Creatinine clearance greater than 50 ml/min
17. Therapy within the previous 28 days before study drug administration with:
17.1. Other biological agents, e.g. anti-TNF, interferon, monoclonal antibodies, growth factor, cytokines
17.2. Other DMARDs (e.g. oral or injectable gold, chloroquine, hydroxychloroquine, cyclosporine, azathioprine, leflunomide, sulfasalazine, D-penicillamine, alkylating agents, e.g. cyclophosphamide, chlorambucil)
18. Doses of prednisolone greater than 10 mg/d within the previous 28 days before study drug administration (week 0)
19. Intra-articular or intra-muscular steroid administration within 28 days before screening. Intra-articular steroid into joint to be scanned/biopsied within 12 weeks of baseline assessments.
20. Previous treatment with total lymphoid irradiation or anti-CD4 or CAMPATH 1-H monoclonal antibodies, resulting in CD4-Lymphopenia and possible immunosuppression (CD4 lymphocytes less than 500/mm^3) or tocilizumab
21. Pregnant women or women of childbearing potential who are unwilling or unable to adhere to an acceptable form of contraception throughout the period of the study timeline. Pregnancy must be excluded before start of treatment with the study drug.
22. Breast-feeding
23. Male patients of procreation potential who are not using reliable contraception during treatment with the study drug
24. History of hypersensitivity to the study medication or to drugs with similar chemical structures or to any of the contents in the tablets (especially previous Stevens - Johnson syndrome, toxic epidermal necrolysis, erythema multiform)
25. History of drug or alcohol abuse
26. Any known condition or circumstance which would prevent compliance or completion of the study, scheduled or anticipated surgery (particularly surgery to the involved knee joint within the study period)
27. Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol
28. Planned surgery within 12 months of study initiation
29. Treatment with any investigational drug in the last 90 days before study entry
30. Any contra-indication to magnetic resonance imaging (MRI) such as pacemaker as per local protocol
31. Female patients will only be enrolled into the study if they are of non-child bearing potential (surgically sterile or at least 2 years postmenopausal) or have satisfied the investigator as having an adequate form of contraception
32. Male patients must consent to practice contraception during the study

Date of first enrolment

01/04/2009

Date of final enrolment
01/11/2009

Locations

Countries of recruitment
United Kingdom

England

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

Sponsor information

Organisation
University of Leeds (UK)

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Industry

Funder Name
Roche Pharmaceuticals (UK)

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?
Abstract results	abstract	01/06/2016	20/05/2019	No	No
Basic results			20/05/2019	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes