ISRCTN95363507 https://doi.org/10.1186/ISRCTN95363507

Tocilizumab in anti-TNF refractory patients with juvenile idiopathic arthritis (JIA) associated uveitis

Submission date
10/06/2015

Recruitment status
No longer recruiting

Registration date
10/06/2015

Overall study status
Completed

Last Edited
10/07/2023

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol

Background and study aims
Juvenile idiopathic arthritis (JIA) is a form of arthritis that develops in children under 16. The cause of the disease is unknown. Symptoms include inflammation, pain and swelling of the joints. There are a number of forms of JIA, including oligoarticular JIA, polyarticular JIA and systemic onset JIA. Eye problems are common and include uveitis, a condition where there is swelling of the middle layer of the eye. Symptoms of uveitis include painful, red eyes, blurred vision, floaters and loss of peripheral vision. It is not a common condition but is still a leading cause of visual impairment in the UK. Here, we want to conduct a study to test whether adding tocilizumab to methotrexate (MTX) treatment will prevent the serious complications, such as glaucoma, cataracts and detached retina that can occur from uncontrolled uveitis in children with JIA. We wish to test the response rate to tocilizumab in combination with MTX and determine whether further research into this treatment for severe, refractory uveitis should be done.

Who can participate?
Children aged between 2-18 years with JIA and severe uveitis who have not responded or are not getting better on anti -TNF therapy (drugs such as adalimumab and infliximab)

What does the study involve?
All children taking part in this study are given tocilizumab injections every 2 weeks or 3 weeks as well as MTX treatment. The dosage for each child is calculated according to their body weight. Response to the treatment is reviewed after 3 months.

What are the possible benefits and risks of participating?
The NHS and its patients would benefit from this trial because patients will be the first worldwide to have access to this novel biological agent within the context of a combined hospital clinic with ophthalmologists and paediatric rheumatologists. Tocilizumab may affect the immune system (your body's natural defences) and you may be more likely to get infections. Tocilizumab can also increase cholesterol levels, which will be monitored during the course of the study at each visit. Some other common side effects of Tocilizumab are

a cough or a sore throat, a blocked or runny nose, a headache or dizziness, mouth ulcers, conjunctivitis, high blood pressure, weight gain or swollen ankles, skin rashes, infections or itching, stomach irritation (gastritis), inflammation around the drip/ injection site.

Where is the study run from?
Six NHS hospitals in the UK

When is the study starting and how long is it expected to run for?
August 2015 to January 2018

Who is funding the study?
Arthritis Research UK

Who is the main contact?
Mr Ben Hardwick

Contact information

Type(s)
Scientific

Contact name
Mr Ben Hardwick

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Additional identifiers

Clinical Trials Information System (CTIS)
2015-001323-23

Protocol serial number
19096

Study information

Scientific Title
A phase II trial of tocilizumab in anti-TNF refractory patients with JIA associated uveitis

Acronym

APTITUDE

Study objectives
This study aims to test whether adding tocilizumab to methotrexate treatment for children with severe uveitis will enable us to prevent the serious complications that can occur from uncontrolled uveitis in children with juvenile idiopathic arthritis (JIA).

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London - South East, ref: 15/LO/0771

Study design
Non-randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Children, Ophthalmology, Musculoskeletal disorders; Subtopic: All Diagnoses, Eye (all Subtopics), Musculoskeletal (all Subtopics); Disease: All Diseases, Non-inflammatory Joint Disorders, Other

Interventions
All participants will receive tocilizumab injections every 2 weeks or every 3 weeks (dependent upon weight) of tocilizumab alongside methotrexate (MTX) treatment. The dosage will be calculated based on patient body weight.
Study Entry : Registration only

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
The primary endpoint is response to treatment. Response to treatment is defined as per SUN criteria as a 2 step decrease in the level of inflammation (anterior chamber cells) or decrease to zero between baseline (prior to trial treatment initiation) and after 12 weeks of treatment.

Key secondary outcome(s))
1. Safety, tolerability and compliance
1.1. Adverse events (AEs), serious adverse events (SAEs) and Adverse Events of Special Interest (AESI)

1.2. Laboratory parameters (haematological and biochemical analysis and urinalysis)
1.3. Participant diaries and dosing records will determine tolerability and compliance throughout the trial treatment period
2.Use of Corticosteroids over duration of study period and throughout follow up, including:
2.1. Total oral corticosteroid dose
2.2. Reduction in and rate of systemic corticosteroid dose from entry dose
2.3. Topical corticosteroid use (frequency) compared to usage at registration.
3. Optic and Ocular
3.1. Visual acuity measured by Age-appropriate LogMar assessment
3.2. Number of participants with resolution of associated optic nerve or macular oedema (as assessed by slit lamp biomicroscopy or optical coherence tomography (OCT)).
3.3. Number of patients who are able to reduce topical or systemic agents for ocular hypertension
3.4. Number of participants with disease control (defined as zero cells, with topical treatment at 12 weeks treatment visit and 24 weeks treatment visit.)
3.5. Number of participants entering disease remission (defined as zero cells, without topical treatment at 12 and 24 weeks treatment visit)
3.6. Duration of sustaining inactive disease (zero cells, with or without topical treatment.)
3.7. Failure to reduce eye drops to 2 drops/day by or at the 12 weeks visit
4. Quality of Life assessment (Childhood Health Questionnaire (CHQ), Childhood Health Assessment Questionnaire (CHAQ))
5. American College of Rheumatology (ACR) Pedi core set criteria: at ACR30, ACR50, ACR70, ACR90 and ACR100 levels
6. Number participants requiring change in biologic / Disease-modifying anti-rheumatic drugs (DMARDs) therapy due to disease flare of their arthritis or failure to respond to treatment for their arthritis
7. Number of participants undergoing flare of arthritis, in remissions on and off medication of their JIA and with minimum disease activity

Completion date
01/04/2019

Eligibility

Key inclusion criteria
1. Children and young people aged at least 2 and 18 years fulfilling ILAR diagnostic criteria for JIA (all subgroups that have uveitis)
2. At the time of trial screening the participant must have active anterior uveitis, defined as a “sustained grade of cellular infiltrate in anterior chamber of SUN criteria grade =1+ or more during the preceding 6 weeks treatment
3. Participants must have failed MTX (minimum dose of 10mg/m2, with a maximum dose of 20mg /m2 and not to exceed 25mg/participant) The participant must have been on MTX for at least 12 weeks and have been on a stable dose of MTX for 4 weeks prior to screening visit
4. Participants must have failed an anti TNF agent (including etanercept, infliximab, golimumbab, certolizumab pegol or adalimumab) and have been on at least one anti-TNF agent regardless of dose for at least 12 weeks at any time previously
5. If a patient has received previous treatment with any of the following biologic agents, these must have been discontinued according to the following timelines prior to registration:
Infliximab 8 weeks prior to registration:
5.1. Etanercept 2 weeks prior to registration
5.2. Adalimumab 4 weeks prior to registration

5.3. Abatacept 8 weeks prior to registration
5.4. Canakinumab 20 weeks prior to registration
5.5. Rilonacept 6 weeks prior to registration
5.6. Anakinra 1 week prior to registration
If a patient has been on another biologic agent not listed above then please contact the trial team for appropriate washout period
6. Written informed consent of participant or parent/legal guardian, and assent where appropriate.
7. Participant and parent/legal guardian willing and able to comply with protocol requirements.
8. For participants of reproductive potential (males and females), use of a reliable means of contraception throughout their trial participation (abstinence is an acceptable method of contraception as long as this is the usual and preferred lifestyle of the patient)
9. Post pubertal females must have a negative serum pregnancy test within 10 days prior to registration
10. Able to commence trial treatment within 2 weeks of the screening visit
Target Gender: Male & Female; Upper Age Limit 18 years ; Lower Age Limit 4 years

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
2 years

Upper age limit
18 years

Sex
All

Total final enrolment
22

Key exclusion criteria
1. Uveitis without a diagnosis of JIA
2. Currently on tocilizumab or has previously received tocilizumab.
3. Participation in another clinical trial of investigational medicinal product within the last 4 weeks or 5 serum half- lives(whichever is longer)
4. More than 6 topical steroid eye drops per day per eye at time of screening
5. For patients on prednisone or prednisone equivalent, change of dose within 30 days prior to registration
6. For patients on prednisone or prednisone equivalent with a dose >0.2mg/kg per day
7. No intraocular injection of disease modification agents including steroids and anti-VEGF within 6 months prior to registration.
8. No intraocular surgery for previous 12 weeks or expected/panned for duration of study.
9. Lack of recovery from recent surgery or surgery < 6 weeks at the time of registration

10. Intra-ocular pressure = 25mm Hg at time of screening.
11. On anti-glaucoma medications
12. No disease modifying immunosuppressive drugs, other than MTX in the 4 weeks prior to registration
13. History of active tuberculosis of less than 6 months treatment or untreated latent TB (a test for latent tuberculosis infection (LTBI) must be performed within twelve weeks prior to registration.
14. Latent TB not successfully treated for at least 4 weeks prior to registration
15. Autoimmune, rheumatic disease or overlap syndrome other than JIA.
16. Females who are pregnant, lactating, or intending to become pregnant during trial
17. Known human immunodeficiency virus infection or other condition characterized by a compromised immune system
18. Any history of alcohol or drug abuse within 6 months prior to registration
19. Any active acute, subacute, chronic, or recurrent bacterial, viral, systemic fungal, infection or any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 4 weeks of registration or treatment with oral antibiotics within 2 weeks of registration
20. History of reactivation or new onset of a systemic infection such as herpes zoster or Epstein-Barr virus within 2 months prior to registration
21. Hepatitis B surface antigen or hepatitis C antibody positivity or chronic viral or autoimmune hepatitis
22. History of concurrent serious gastrointestinal disorders
23. Evidence of current serious uncontrolled concomitant cardiovascular (including hyperlipidemia), nervous system,pulmonary (including obstructive pulmonary disease), renal and hepatic disease
24. History of or current cancer or lymphoma
25. Persistently poorly controlled severe hypertension (>95th percentile for height / age)
26. Uncontrolled diabetes mellitus
27. History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies
28. No live attenuated vaccines (including seasonal nasal flu vaccine, varicella vaccine for shingles or chickenpox, MMR or MMRV, oral polio vaccine and vaccines for yellow fever, measles, mumps or rubella) 4 weeks prior to registration, throughout the duration of the trial and for 8 weeks following the last dose of study drug
29. Immunization with a live/attenuated vaccine within 4 weeks prior to registration
30. Previous treatment with any cell depleting therapies, including investigational agents or approved therapies (e.g.CAMPATH, anti-CD4, anti-CD5, anti- CD3, anti-CD19 and anti-CD20)
31. Treatment with intravenous gamma globulin or plasmapheresis within 24 weeks of registration
32. Any previous treatment with alkylating agents such as chlorambucil, or with total lymphoid irradiation
33. Any significant medical or surgical condition that would risk the patient’s safety or their ability to complete the trial
34. Any psychological condition that in the opinion of the principal investigator would interfere with safe completion of the trial
35. Demonstrations of clinically significant deviations from the following laboratory parameters:
35.1 Serum creatinine > 1.5 × the upper limit of normal (ULN) for age and sex
35.2. AST or ALT > 1.5 × the ULN for age and sex
35.3. Total bilirubin > 1.3 mg/dL (>23 µmol/L)
35.4. Platelet count < 150 × 103/µL (< 150,000/mm3)
35.5. Hemoglobin < 7.0 g/dL (< 4.3 mmol/L)
35.6. White blood cell (WBC) count < 5,000/mm3 (< 5.0 × 109/L)
35.7 Neutrophil count < 2,500/mm3 (< 2.5 × 109/L)

Date of first enrolment
01/08/2015

Date of final enrolment
01/01/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Bristol Royal Hospital for Children (Lead Centre)
Bristol
United Kingdom
BS2 8BJ

Study participating centre
Great Ormond Street Hospital
London
United Kingdom
WC1N 3JH

Study participating centre
Alder Hey Children's Hospital
Liverpool
United Kingdom
L12 2AP

Study participating centre
Southampton Children's Hospital
Southampton
United Kingdom
SO16 6YD

Study participating centre
Great North Children's Hospital
Newcastle

United Kingdom
NE1 4LP

Study participating centre
Sheffield Children's Hospital
Sheffield
United Kingdom
S10 2TH

Sponsor information

Organisation
University Hospitals Bristol NHS Foundation Trust

ROR
https://ror.org/04nm1cv11

Funder(s)

Funder type
Charity

Funder Name
Arthritis Research UK

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	07/02/2020	15/04/2020	Yes	No
Protocol article	protocol	27/02/2018	20/03/2019	Yes	No
HRA research summary			28/06/2023	No	No
Statistical Analysis Plan		27/02/2018	10/07/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes