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The clinical effectiveness, safety and cost effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis

Submission date
02/09/2011

Recruitment status
No longer recruiting

Registration date
02/09/2011

Overall study status
Completed

Last Edited
30/04/2019

Condition category
Eye Diseases

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

Plain English summary of protocol

Background and study aims
Arthritis is a common condition which causes pain and swelling (inflammation) in the joints. Arthritis is usually associated with older people, but it can also affect children. Most cases of arthritis in children are known as juvenile idiopathic arthritis (JIA), because the cause is not known (idiopathic). In order to be diagnosed with JIA, one or more joints must be inflamed for more than 6 weeks, in a child under the age of 16. Children suffering from JIA have a higher risk of developing inflammation in other parts of the body. One of the most common is inflammation of the middle layer of the eye, called the uvea (uveitis). If uveitis is not treated, then it can lead to permanent damage to the eye and even blindness. Methotrexate is a drug that is commonly prescribed to children suffering from JIA-associated uveitis as, although it is not a cure, it can help to reduce the inflammation. It has been found that in many children treated with methotrexate, the inflammation to the uvea cannot be completely controlled, and they eventually become blind. A possible way of helping these children is to better treat the underlying cause of the inflammation, rather than just the symptoms. In the body, sometimes the proteins that are meant to help fight infections can attack our own cells, leading to inflammation, particularly one called Tumor necrosis factor (TNF). Adalimumab is an “anti-TNF” drug, which reduces inflammation by stopping TNF in the body from working. The aim of this study is to find out whether using adalimumab and methotrexate at the same time is an effective treatment for JIA-associated uveitis.

Who can participate?
Children between the ages of 2 and 18 years old with active JIA-associated uveitis, despite treatment with methotrexate for at least 12 weeks.

What does the study involve?
Participants are randomly allocated into two groups. Those in the first group (intervention group) are given subcutaneous (under the skin) injections of adalimumab every two weeks for 18 months, as well as continuing their normal methotrexate treatment. Participants in the second

group (control group) are given subcutaneous (under the skin) injections of a placebo (inactive medicine) every two weeks for 18 months, while continuing their methotrexate treatment. The effectiveness of the treatment for both groups is monitored for another 18 months after the treatment ends.

What are the possible benefits and risks of participating?
Not provided at time of registration.

Where is the study run from?
Institute of Child Health, Liverpool (UK)

When is the study starting and how long is it expected to run for?
October 2011 to October 2015

Who is funding the study?
1. Arthritis Research UK (UK)
2. Health Technology Assessment Programme (UK)

Who is the main contact?
Mr Ben Hardwick

Contact information

Type(s)
Scientific

Contact name
Mr Ben Hardwick

Contact details
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Additional identifiers

Clinical Trials Information System (CTIS)
2010-021141-41

Protocol serial number
10320

Study information

Scientific Title

Randomised controlled trial of the clinical effectiveness, SafetY and Cost effectiveness of Adalimumab in combination with MethOtRExate for the treatment of juvenile idiopathic arthritis associated uveitis

Acronym
SYCAMORE

Study objectives
To compare the clinical effectiveness of adalimumab in combination with methotrexate (MTX) versus placebo with MTX alone, with regard to controlling disease activity in refractory uveitis associated with juvenile idiopathic arthritis (JIA).

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London (Hampstead), 24/06/2011, ref: 11/LO/0425

Study design
Single-centre randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Ophthalmology

Interventions
Adalimumab is a fully human monoclonal antibody engineered by gene technology that uses site-directed mutagenesis to enhance its binding efficiency to TNF.

Adalimumab group: All patients will receive subcutaneous injections of Adalimumab every two weeks for 18 months. Patients will then for followed up for a further 18 months. All patients will continue to receive a stable dose of Methotrexate throughout the trial. Patients will have previously been taking Methotrexate before entry into the trial.

Placebo group: All patients will receive subcutaneous injections of Placebo every two weeks for 18 months. Patients will then for followed up for a further 18 months. All patients will continue to receive a stable dose of Methotrexate throughout the trial. Patients will have previously been taking Methotrexate before entry into the trial.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
1. Adalimumab 2. Methotrexate

Primary outcome(s)
Main outcome measure: time to treatment failure

Treatment failure is defined by ONE or more of the following:
1. Anterior segment inflammatory score grade (SUN criteria), following at least 3 months of therapy:
1.1. 2-Step increase in SUN cell activity score (AC Cells) over 2 consecutive readings
1.2. Sustained non-improvement with entry grade of 3 or greater for 2 consecutive readings
1.3. Only partial improvement (1 grade) with sustained development of other ocular co-morbidity*
1.4. Sustained scores as recorded at entry grade measured over 2 consecutive readings (grades 0.5 to 2) still present after 6 months of therapy
1.5. Worsening of existing (on enrolment) ocular co-morbidity after 3 months
2. Use of concomitant medications: At any time, requirement to use concomitant medications in manner out with pre-defined acceptable criteria, or any of the concomitant medications not allowed

* Ocular co-morbidities are defined as:
1. Disc swelling and/or Cystoid Macular Oedema (CMO) as gauged clinically and where possible by OCT evidence; and/or:
2. Sustained raised intraocular pressure (<25mm Hg) over 1 month not responding to single ocular hypotensive agent, and/or:
3. Sustained hypotony (<6 mm Hg) over 1 month, and/or
4. Development of unexplained reduction in vision (LogMar) of 15 letters (in the event of cataract participants will remain in trial, also if cataract surgery is required. Failure will still remain as described in endpoints above).

2. Use of concomitant medications: At any time, requirement to use concomitant medications in manner out with pre-defined acceptable criteria, or any of the concomitant medications not allowed

Key secondary outcome(s))
1. Number of participants failing treatment
2. Incremental cost-effectiveness and cost-utility of adalimumab added to MTX compared with MTX alone
3. Health status according to the multi-attribute health utility index, HUI2
4. Safety, tolerability and compliance
4.1. Adverse events (AEs) and serious adverse events (SAEs)
4.2. Laboratory parameters (haematological and biochemical analysis and urinalysis
4.3. Development of anti-adalimumab antibody (HAHA) will be determined with samples collected at months 1, 6 and 18
4.4. Participant diaries and dosing records will determine tolerability and compliance throughout the trial treatment period
5. Use of Corticosteroids over duration of study period and throughout follow up, including:
5.1 Total oral corticosteroid dose
5.2. Reduction in and rate of systemic corticosteroid dose from entry dose
5.3. Topical corticosteroid use (frequency) compared to entry usage
5.4. Need for pulsed corticosteroid

6. Optic and ocular
6.1. Number of participants having disease flares (as defined by worsening on SUN criteria) following minimum 3 months disease control
6.2. Number of participants having disease flares within the first 3 months.
6.3. Visual acuity measured by Age-appropriate LogMar assessment
6.4. Visual angle improvement: defined as number of participants halving visual angle
6.5. Visual angle worsening: defined as number of participants doubling visual angle
6.6. Number of participants with resolution of associated optic nerve or macular oedema (as assessed by slit lamp biomicroscopy or optical coherence tomography (OCT) (where available)
6.7. Number of participants with disease control (defined as zero cells, with topical treatment for 3 and 6 months)
6.8. Number of participants entering disease remission (defined as zero cells, without topical treatment for 3 and 6 months)
6.9. Duration and magnitude in sustaining inactive disease (zero cells, with or without topical treatment)
7. Quality of Life assessment (Childhood Health Questionnaire (CHQ), Childhood Health Assessment Questionnaire (CHAQ))
8. American College of Rheumatology (ACR) Pedi core set criteria: at ACR30, ACR50, ACR70, ACR90 and ACR100 level
9. Number of participants undergoing disease flare, in remission on and off medication 54 of their JIA and with minimum disease activity 55
10. Number participants requiring change in biologic / Disease-modifying anti-rheumatic drugs (DMARDs) therapy due to failure to respond from arthritis

Completion date
01/10/2015

Eligibility

Key inclusion criteria
Inclusion criteria as of 20/12/2016:
1. Children and young people aged ≥ 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 12 weeks therapy despite MTX and corticosteroid (both systemic and topical) therapy”. The latest date of SUN grade score must be the date of the screening visit
3. They must have failed MTX (minimum dose of 10-20mg/m2, with a maximum dose of 25mg /participant). The participant must have been on MTX for at least 12 weeks* and have been on a stable dose for 4 weeks prior to screening visit.
4. No Disease modifying immunosuppressive drugs, other than MTX, in the 4 weeks prior to screening
5. Written informed consent of participant or parent/legal guardian, and assent where appropriate
6. Participant and parent/legal guardian willing and able to comply with protocol requirements
7. For participants of reproductive potential (males and females), use of a reliable means of contraception throughout their trial participation. Post pubertal females must have a negative serum pregnancy test within 10 days before the first dose of trial drug.
8. Able to be randomised and commence trial treatment within 2 weeks of the screening visit

* Omission of a maximum of 2 weeks methotrexate treatment within the 12 weeks is acceptable and will not render the patient ineligible unless they have been missed in the 4 weeks prior to the screening visit.

Original inclusion criteria:
1. A participant is eligible for the trials based upon at least one eye fulfilling the eligibility criteria
2. Children and young people aged between 2 and 18 years fulfilling International League of Associations for Rheumatology (ILAR) diagnostic criteria for JIA (all subgroups that have uvietis)
3. At the tie of trial screening the participant must have active anterior uveitis, defined as a sustained grade of cellular infiltrate in anterior chamber of Standardization of Uveitis Nomenclature (SUN) criteria grade =1+ or more during the preceding 12 weeks therapy despite MTX and corticosteroid (both systemic and topical) therapy
4. They must have failed MTX (minimum dose of 10-15mg/m2, with a maximum dose of 25mgs). The participant must have been on MTX for at least 12 weeks* and have been a stable dose for 4 weeks prior to screening visit.
5. Disease modifying immunosuppressive drugs, other than MTX, discontinued at least 4 weeks before receiving the first dose of adalimumab.
6. Written informed consent of participant or parent/legal guardian, and assent where appropriate
7. Participant or 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. Post pubertal females must have a negative serum pregnancy test within 10 days before the first dose of trial drug.
9. Able to be randomised and commence trial treatment within 2 weeks of the screening visit.
*Omission of a maximum of 2 weeks Methotrexate treatment within the 12 weeks is acceptable and will not render the patient ineligible unless they have been missed in the 4 weeks prior to the screening visit.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
2 years

Upper age limit
17 years

Sex
All

Total final enrolment
90

Key exclusion criteria

Exclusion criteria as of 20/12/2016:
1. Uveitis without a diagnosis of JIA
2. Currently on adalimumab or has previously received adalimumab.
3. Have been on other biologic agent within previous 5 half-lives of agent (For other biologic agents and their was out periods
4. More than 6 topical steroid eye drops per eye, per day prior to screening (this dose must have been stable for at least 4 weeks prior to screening visit)
5. For patients on Prednisone or Prednisone equivalent, change of dose within 30 days prior to screening
6. For patients on Prednisone or Prednisone equivalent with a dose >0.2mg/kg per day
7. Intra-articular joint injections within four weeks prior to screening
8. Any ongoing chronic or active infection (including infective uveitis) or any major episode of infection requiring hospitalisation or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days prior to the screening evaluation
9. History of active tuberculosis of less than 6 months treatment or untreated latent TB
10. Participant has history of central nervous system (CNS) neoplasm, active CNS infection, demyelinating disease, or any progressive or degenerative neurological disease
11. Poorly controlled diabetes or persistently poorly controlled severe hypertension (>95th percentile for height / age) as deemed by the treating physician
12. Previous history of malignancy
13. Intraocular surgery within the 3 months prior to screening (cataract/ glaucoma/ vitrectomy)
14. Intra-ocular or peri-ocular corticosteroids within 30 days prior to screening.
15. History of ocular herpetic disease
16. Pregnant or nursing female
17. Demonstrations of clinically significant deviations in any of the following laboratory parameters:
17.1. Platelet count < 100,000/mm3
17.2. Total white cell count < 4000 cells/mm3
17.3. Neutrophils < 1000 cells/mm3
17.4. AST or ALT > 2 x upper limit of normal (ULN) or serum bilirubin > 2x the ULN
17.5. Glomerular filtration rate (GFR) of < 90 mL/min/1.73m2 [GFR (ml.min/1.73 m2 BSA) = 0.55 x height (cm)/plasma creatinine (mg/dl)]
17.6. Hematocrit <24%
18. Having been administered a live or attenuated vaccine within three months prior to screening
19. Previous randomisation into the SYCAMORE trial to either arm of the trial.
20. Intra-ocular pressure <6mm Hg or Intra-ocular pressure > 25mm Hg
21. Intra-ocular pressure control requiring more than one topical pressure lowering therapy or requiring systemic acetazolamide

Original exclusion criteria:
1. Uveitis without a diagnosis of JIA
2. Currently on adalimumab or has previously failed on adalimumab
3. Have been on other biologic agent within previous 5 half-lives of agent (For other biologic agents and their washout periods
4. More than 6 topical steroid eye drops per day at randomisation (this dose must have been stable for at least 4 weeks prior to screening visit)
5. For patients on Prednisone equivalent, change of dose within 30 days prior to randomisation
6. For patients on Prednisone or Prednisone equivalent with a dose >0.2mg/kg per day
7. Intra-articular joint injections within four weeks prior to randomisation
8. Any ongoing chronic or active infection (including infected uveitis) or any major episode of infection requiring hospitalisation or treatment with intravenous antibiotics within 30 days or oral antibiotics within 14 days prior to the screening evaluation

9. History of active tuberculosis of less tan 6 months treatment or untreated latent TB
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19. Previous randomisation into the SYCAMORE trial to either arm of the trial

Date of first enrolment
01/10/2011

Date of final enrolment
01/10/2015

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Institute of Child Health
Alder Hey Children's Hospital
Eaton Road
Liverpool
United Kingdom
L12 2AP

Sponsor information

Organisation

University Hospitals Bristol NHS Foundation Trust (UK)

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

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	27/04/2017		Yes	No
Results article	cost-effectiveness results	01/03/2019		Yes	No
Results article	results	01/04/2019	30/04/2019	Yes	No
Protocol article	protocol	09/01/2014		Yes	No
HRA research summary			28/06/2023	No	No