Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT

Athimalaipet V Ramanan,[1,2]* Andrew D Dick,[3,4,5] Ashley P Jones,[6] Dyfrig A Hughes,[7] Andrew McKay,[6] Anna Rosala-Hallas,[6] Paula R Williamson,[6] Ben Hardwick,[6] Helen Hickey,[6] Naomi Rainford,[6] Graeme Hickey,[6] Ruwanthi Kolamunnage-Dona,[6] Giovanna Culeddu,[7] Catrin Plumpton,[7] Eifiona Wood,[7] Sandrine Compeyrot-Lacassagne,[8] Patricia Woo,[8] Clive Edelsten[8] and Michael W Beresford[9,10] on behalf of the SYCAMORE Study Group

[1]Department of Paediatric Rheumatology, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[2]Bristol Medical School, University of Bristol, Bristol, UK
[3]Bristol Eye Hospital, Bristol, UK
[4]School of Clinical Sciences, University of Bristol, Bristol, UK
[5]University College London Institute of Ophthalmology and National Institute for Health Research (NIHR) Biomedical Research Centre at Moorfields Eye Hospital and University College London Institute of Ophthalmology, London, UK
[6]Department of Biostatistics, Institute of Translational Medicine, University of Liverpool, Liverpool, UK
[7]Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, UK
[8]Great Ormond Street Hospital, London, UK
[9]Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[10]Department of Women's and Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

*Corresponding author avramanan@hotmail.com

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Scientific summary

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Scientific summary

Background

Juvenile idiopathic arthritis (JIA) is the most common paediatric rheumatic disease. Children with JIA are at significant risk of inflammation of the uvea (uveitis). Approximately 12–38% of patients with JIA develop uveitis within 7 years following the onset of arthritis. Despite current screening and therapeutic options, up to 15% of children with JIA-associated uveitis may develop bilateral visual impairment and be certified legally blind.

Experimental models of autoimmune uveitis demonstrate that tumour necrosis factor alpha (TNF-α) plays a pivotal role in pathogenesis, which is borne out in the treatment of adult uveitis and paediatric case series. Adalimumab (Humira®; AbbVie Inc., Ludwigshafen, Germany) is a fully human anti-TNF-α monoclonal antibody. A multicentre randomised, double-blind, parallel-group trial has shown significant benefit in children with active rheumatoid arthritis.

The 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 (SYCAMORE) was conducted to assess the role of adalimumab in the treatment of methotrexate (MTX)-refractory JIA-associated uveitis.

Aims and objectives

The primary objective of the trial was to compare the clinical effectiveness of adalimumab in combination with MTX versus placebo with MTX alone, with regard to controlling disease activity in refractory uveitis associated with JIA.

The secondary objectives of the trial were to:

- evaluate short-term safety and tolerability of adalimumab in combination with MTX versus MTX alone, with regard to ocular complications of treatment, adverse events (AEs) and laboratory assessments
- determine quality of life and cost-effectiveness of adalimumab in combination with MTX versus MTX alone in severe uveitis associated with JIA
- determine the clinical effectiveness of adalimumab in combination with MTX versus MTX alone, with regard to underlying JIA disease activity
- determine the durability and magnitude of adalimumab efficacy response in sustaining inactive disease and achieving complete clinical remission
- determine the long-term safety of adalimumab in combination with MTX versus MTX alone
- assess the efficacy of treatment with adalimumab to permit concomitant medication reduction, in particular regional and parenteral steroids
- develop a fully consented, trial-related tissue bank for subsequent investigation.

Methods

Study design

This was a randomised, parallel-group, double-blind, placebo-controlled, multicentre clinical trial that compared the effects of adalimumab in combination with MTX with placebo in combination with MTX in participants with active uveitis in association with JIA refractory to MTX monotherapy.

Participants were randomised in a ratio of 2 : 1 (in favour of adalimumab) to receive up to 18 months of the randomised treatment. Once treatment had stopped, participants were followed up for a further 6 months. The primary outcome (treatment failure) was assessed by a blinded assessor at each scheduled or unscheduled visit.

The trial also included an economic evaluation to estimate the incremental cost per quality-adjusted life-year (QALY) with adalimumab in addition to MTX, versus MTX alone.

Eligibility criteria

Children and adolescents aged 2–18 years with active JIA-associated uveitis, despite stable MTX treatment for at least 12 weeks, were eligible for randomisation.

Exclusion criteria were previous exposure to adalimumab, previous exposure to another biologic (within five half-lives), receipt of more than six topical glucocorticoid drops per eye per day and receipt of prednisone (or equivalent) at a dose exceeding 0.2 mg/kg of body weight per day.

Recruitment

The trial took place in 17 centres throughout the UK, 14 of which randomised at least one participant.

Randomisation and blinding

Participants were randomised in a 2 : 1 ratio (in favour of adalimumab); randomisation sequences were computer-generated, stratified by centre.

Participants, investigators and study personnel were all blinded to the study medication that the participant received. Pharmacy department staff were not blinded to the study medication that the participant received.

Outcome measures

Primary outcome

The primary end point of the study was ‘time to treatment failure’. ‘Treatment failure’ was defined by the presence of one or more of the following factors:

- Anterior segment inflammatory score grade [Standardisation of Uveitis Nomenclature (SUN) criteria] –
  - two-step increase from baseline in SUN cell activity score (anterior chamber cells) over two consecutive readings
  - sustained non-improvement with entry grade of ≥ 3 for two consecutive readings
  - only partial improvement (1+ grade) or no improvement from baseline, with development of other ocular comorbidities (defined below) that are sustained
  - worsening of existing (on enrolment) ocular comorbidities (defined below) after 3 months
  - sustained scores recorded at entry grade, measured over two consecutive readings (grade 1 or 2) and still present after 6 months of therapy.

In addition, following at least 3 months of therapy, treatment failure was met if any of the following factors were met:

- Use of concomitant medications – at any time, requirement for concomitant medications in a manner outside the predefined acceptable criteria or for any of the concomitant medications not allowed.
- Intermittent or continuous suspension of study treatment (adalimumab or placebo) for a cumulative period of longer than 4 weeks.
- Ocular comorbidities, defined as:

  i. disc swelling and/or cystoid macular oedema (as gauged clinically and when possible by optical coherence tomography evidence)
  ii. raised intraocular pressure (IOP) (> 25 mmHg) sustained over two consecutive visits (not responding to a single ocular hypotensive agent)
  iii. hypotony (< 6 mmHg) sustained over two consecutive visits
  iv. development of an unexplained reduction in vision over two consecutive visits of 0.3 logarithm of the minimum angle of resolution (logMAR) units (in the event of cataracts, participants will remain in the trial; if cataract surgery is required, failure will still remain as described in end points above)

Please note that an IOP of ≥ 25 mmHg or < 6 mmHg was an exclusion criterion at baseline. Ocular comorbidities (i)–(iv) could be developed during follow-up only; (i) may worsen based on the existing (on enrolment) ocular comorbidity.

Secondary outcomes

- Number of participants failing treatment.
- Incremental cost-effectiveness of adalimumab added to MTX, compared with MTX alone.
- Health status according to the multiattribute Health Utility Index Mark 3 (HUI3).
- Safety, tolerability and compliance defined as follows:

  - AEs and serious adverse events (SAEs)
  - laboratory parameters (haematological and biochemical analysis and urinalysis)
  - participant diaries and dosing records determined tolerability and compliance throughout the trial treatment period.

- Use of corticosteroids over the duration of the study period and throughout follow-up, including the following:

  - total oral corticosteroid dose
  - reduction and reduction rate of systemic corticosteroid dose from entry dose
  - topical corticosteroid use (frequency) compared with use at time of entry
  - need for pulsed corticosteroid.

- Optic and ocular outcomes, defined as follows:

  - number of participants with disease flares (defined by worsening based on SUN criteria) following a minimum of 3 months of disease control
  - number of participants with disease flares within the first 3 months of the study
  - visual acuity as measured by age-appropriate logMAR assessment
  - number of participants with resolution of associated optic nerve or macular oedema [as assessed by slit lamp biomicroscopy or optical coherence tomography (when available)]
  - number of participants with disease control (defined as zero cells with topical treatment for 3 and 6 months)
  - number of participants entering disease remission (defined as zero cells without topical treatment for 3 and 6 months)
  - duration of sustaining inactive disease (zero cells with or without topical treatment).

- Quality-of-life assessments [as assessed via the Childhood Health Questionnaire (CHQ) and Childhood Health Assessment Questionnaire (CHAQ)].
- American College of Rheumatology (ACR) Pedi core set criteria at ACR 30, 50, 70, 90 and 100 levels.
- Number of participants with disease flares, in remission on and/or off medication, related to their JIA and with minimum disease activity.
- Number of participants requiring change in biological and/or disease-modifying antirheumatic drug therapy for arthritis due to failure to respond.
- Juvenile Arthritis Disease Activity Score.

Sample size

The total target number of participants was 114 (adalimumab, $n = 76$; placebo with MTX, $n = 38$).

Statistical methods

Primary and secondary outcome data were analysed following the intention-to-treat (ITT) principle. Safety analyses included participants' data if they had received at least one dose of the randomised treatment.

The statistical analysis plans were developed prior to the analyses being conducted.

The primary outcome was 'time to treatment failure' and was analysed at two planned interim analyses; the final analysis used Kaplan–Meier curves and the log-rank test. Nine predefined sensitivity analyses were conducted to test the robustness of the primary analyses to different assumptions.

The secondary outcomes were analysed using the following methods: binary outcomes were analysed using the chi-squared test, time-to-event data and longitudinal data were analysed using joint modelling, time-to-event data with competing risks were analysed using a competing risk model, continuous data were analysed using *t*-tests or random intercept models and count data were analysed using Poisson regression.

Economic analysis

The economic analysis adopted the perspective of the NHS in England and Personal Social Services providers. Resource use was estimated using questionnaires and via medical records, and utilities were estimated via the HUI3 multiattribute utility scoring system. Costs were based on 2016 prices, and both costs and QALYs were discounted at 3.5% after the first year. Missing utility data were handled using multiple imputation. Costs and QALYs were analysed using an instrumental variable regression approach to account for patients having access to adalimumab during the open-label phase of the trial. A trial-based evaluation, based on the ITT population, was extrapolated by 10 years using a Markov model in order to assess the long-term costs and consequences of adalimumab treatment. The primary outcome of the economic evaluation was the incremental cost per QALY with adalimumab in addition to MTX versus MTX alone. Probabilistic sensitivity analyses assessed the impact of parameter uncertainty, and scenario analyses were conducted to assess the impact of varying (1) the proportion of patients continuing adalimumab after the end of the study; (2) the duration of post-study access to adalimumab; (3) patient adherence to adalimumab and MTX; (4) the time horizon of analysis; (5) the unit price of adalimumab; (6) visual impairment rates, using the most and least favourable combinations; and (7) the discount rate of future costs and benefits.

Results

Recruitment to the trial was halted based on the results of the second interim analysis of the trial data. These data showed that there was significant evidence that adalimumab was more effective than placebo. The Independent Data and Safety Monitoring Committee (IDSMC) made the recommendation to stop recruitment and unblind the participants who were on trial treatment at that time. Participants who were on placebo stopped taking their randomised treatment and entered the follow-up period of the trial; participants who were on adalimumab continued with their treatment as per the protocol.

The trial had three distinct phases: the double-blind phase of the trial refers to the period of time that participants were on treatment prior to the IDSMC recommending that unblinding of allocations should take place; the open-label phase of the trial refers to the period of time that participants were on treatment following the IDSMC recommendation to unblind treatment allocations (this phase of the trial only contained participants who were on adalimumab); and the follow-up phase of the trial is the period of time that followed discontinuation of treatment.

The total number of participants analysed was 90 (adalimumab, $n = 60$; placebo, $n = 30$).

The analysis of the data from the double-blind phase of the trial showed that the hazard of treatment failure was significantly reduced by 75% for participants in the adalimumab group [hazard ratio (HR) 0.25, 95% confidence intervals (CI) 0.12 to 0.51; $p < 0.0001$ from log-rank test]. Additional data collected during the open-label phase of the trial continued to support this conclusion for the integrated analysis of the double-blind and open-label data. The results of the sensitivity analyses showed that the conclusions of the primary analysis were robust to changes that were made. These results all remained highly statistically significant.

The results of the analysis of the secondary outcomes strengthen the evidence to support the effectiveness of adalimumab over placebo.

Adalimumab-treated patients had a much higher incidence of AEs and SAEs. However, this difference was not deemed to be clinically significant and the differences observed between the adalimumab and placebo groups in terms of the frequency of AEs and SAEs, or for the laboratory parameters, were as expected for this population. Data collected during the follow-up period for laboratory parameters continued to show no clinically significant differences between the two treatment groups.

The total costs associated with adalimumab treatment over the time horizon of the 18-month trial plus 10-year extrapolation were £70,951 [95% credible range (CR) £45,204 to £123,764] The corresponding costs of the placebo arm were £31,587 (95% CR £5308 to £83,320). Total mean QALYs were 8.60 (95% CR 8.00 to 9.19) and 8.29 (95% CR 7.42 to 9.17) for the adalimumab and placebo arms, respectively. The incremental cost-effectiveness ratio (ICER) was £129,025 per QALY gained. In 96% of simulations, adalimumab was both more costly and more effective; however, the probability of cost-effectiveness at the £30,000 per QALY threshold was < 1%.

Conclusions

Adalimumab significantly controlled inflammation and reduced the rate of treatment failure in patients with active uveitis on a stable dose of MTX. Adalimumab-treated patients had a much higher incidence of AEs and SAEs, and the treatment is not cost-effective at the £30,000-per-QALY threshold.

Recommendations for future research

This trial demonstrated effective achievement of inactive disease using a combination of adalimumab and MTX. A clinical trial is now needed to determine which treatment regimen (continuing or stopping adalimumab) will result in shorter time to recurrence of ocular inflammation in patients with quiescent JIA-associated uveitis.

There is also a need to identify effective clinical biomarkers of early and complete response.

Trial registration

This trial is registered as ISRCTN10065623 and European Clinical Trials Database EudraCT number 2010-021141-41.

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