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Efficacy and safety of adalimumab for inflammatory flare prevention in paediatric non-infectious anterior uveitis with peripheral retinal vascular leakage: a study protocol for a single-centre, randomised controlled trial

Hang Song [1], Chan Zhao,[1] Yuelun Zhang [2], Donghui Li,[1] Yujing Qian,[1] Fei Gao,[1] Junyan Xiao,[3] Meifen Zhang[1]

For numbered affiliations see end of article.

Correspondence to
Dr Meifen Zhang;
meifen_zhang@hotmail.com

ABSTRACT

Introduction Paediatric patients with chronic anterior uveitis are more prone to suffer from the chronic course of intraocular inflammation and adverse effects of long-term immunomodulatory therapy, either topical glucocorticosteroids or systemic immunomodulatory agents. The performance of adalimumab has been shown to be fairly favourable in treating refractory non-infectious uveitis, but the detailed indication is still under investigation. This study aims to assess the efficacy and safety of adalimumab for inflammatory flare prevention in non-infectious paediatric anterior uveitis with peripheral retinal vascular leakage, compared with methotrexate.

Methods and analysis Children weighed ≥30 kg and aged between 4 and 16 years old with active non-infectious anterior uveitis with peripheral retinal vascular leakage on ultra-wildfield fluorescein fundus angiography will be included. They will be treated with a predesigned inflammatory control regimen to reach inflammatory quiescence in 1 month. After that they will be treated with either methotrexate 10 mg once a week or adalimumab once every 2 weeks and regularly followed up for 6 months. The primary endpoint is uveitis flare defined as defined as anterior chamber cell count grading increased from 0 to 1 within the observation period.

Ethics and dissemination The study was approved by the Institutional Review Board of Peking Union Medical College Hospital, Beijing, China (Approved protocol V3, dated 27 July 2021. Approval number 25-ZS-3062) and has been registered on ClinicalTrials.gov. Written informed consent will be collected from every patient and their guardians prior to study participation. The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication.

Trial registration number NCT05015335.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a prospective, single-centre, open-label, randomised controlled trial.
⇒ Children weighed ≥30 kg aged between 4 and 16 years old with active non-infectious anterior uveitis and peripheral retinal vascular leakage will be included.
⇒ After active inflammation is controlled, participates will be treated with either methotrexate 10 mg once a week or adalimumab once every 2 weeks.
⇒ The primary endpoint is uveitis flare defined as anterior chamber cell count grading increased from 0 to 1.

therapies pose children at risk of their side effects, such as secondary glaucoma[1] and cataract caused by topical steroids, growth retardation and weight gain caused by oral glucocorticosteroids (GCs), hepatotoxicity and bone marrow suppression caused by the first choice immunosuppressor, methotrexate.[2] Adalimumab, a humanised recombinant antibody directed against soluble and cell-bound tumour necrosis factor-alpha (TNF-α), has increasingly been recognised as a promising agent for treating noninfectious uveitis in adults[3 4] and children.[5]

There have been several randomised clinical trials (RCTs) regarding to the efficacy and safety of adalimumab in treating active inflammation in paediatric uveitis. For example, SYCAMORE trial included 90 paediatric juvenile idiopathic arthritis (JIA)-associated uveitis patients who had failed treatment with topical or systemic GCs and methotrexate. Twenty-seven per cent of patients in the adalimumab group vs 60% in the placebo group

INTRODUCTION

Paediatric uveitis is usually a long-lasting, recurrent intraocular inflammation that may lead to early onset visual disability. Traditional

came across treatment failure in the 18 months observation period (HR, 0.25; 95% CI 0.12 to 0.49).[6] The ADJU-VITE trail included 32 patients with childhood-onset anterior uveitis and an inadequate response to topical GCs and methotrexate. After 2 months, 56.3% of patients responded to treatment in the adalimumab group compared with 20% in the placebo group (p=0.038; relative risk=2.81, 95% CI 0.94 to 8.45; risk difference: 36.3%, 95% CI 2.1% to 60.6%).[7] These RCTs provided compelling evidence that adalimumab is effective in paediatric uveitis. However, detailed indications, timings and durations of adalimumab treatment and the disease monitoring parameters for paediatric uveitis are still not clear.[8]

We designed an RCT that focuses on paediatric anterior uveitis with peripheral retinal vascular leakage, demonstrated by the ultra-wildfield fluorescein fundus angiography (UWFFA). We will investigate the efficacy of adalimumab to prevent inflammatory flare in those patients, compared with the traditional methotrexate therapy.

METHODS AND ANALYSIS
Overview of design
This is a prospective, single-centre, open-label, randomised controlled trial that will be performed at Department of Ophthalmology, Peking Union Medical College Hospital. The aim of the study is to investigate the superiority of adalimumab over methotrexate in preventing inflammatory flare in non-infectious paediatric anterior uveitis and its safety profiles. The study is registered on ClinicalTrials. gov and is in full compliance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol has been designed according to the Standard Protocol Items: Recommendations for Interventional Trials checklist. The study design is depicted in figure 1.

Study subjects
Patients who meet all of the following inclusion criteria will be recruited in this trial.
1. Children with non-infectious anterior uveitis aged between 4 and 16, weight ≥30 kg.
2. Uveitis resistant to well conducted topical GCs therapy for 3 months, or uveitis resistant to well conducted prednisolone acetate twice a day for 1 month.
3. Peripheral retinal vascular leakage demonstrated by UWFFA at the time of inclusion.

Patients who meet any of the following exclusion criteria will be excluded from this trial.
1. Any contraindication for administration of immunosuppressive therapy (active tuberculosis, immune deficits, opportunistic infections, other severe chronic diseases).
2. Previous diagnosis or signs of demyelinating disease of the central nervous system.
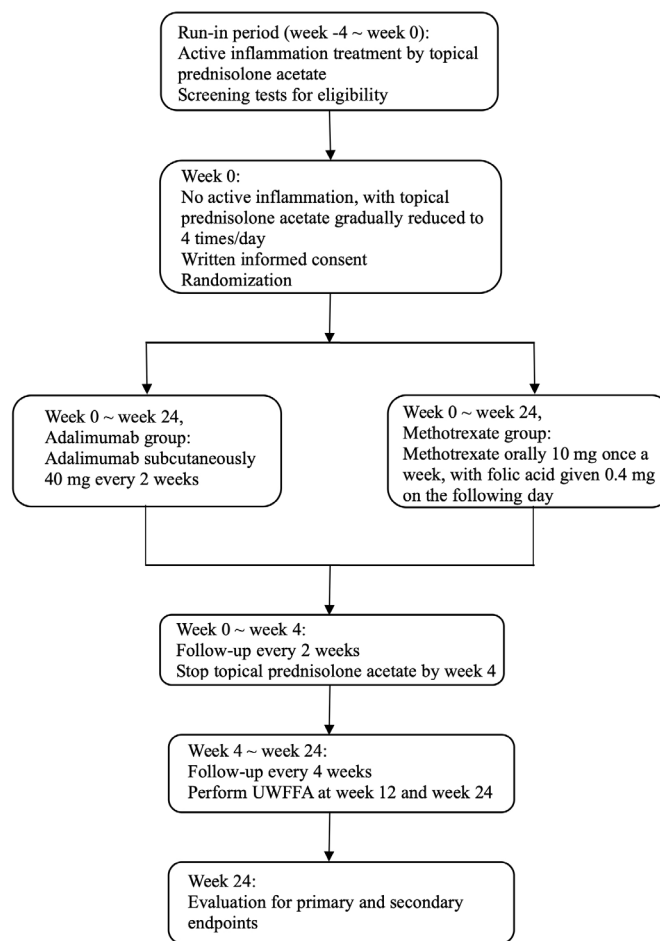3. Children unable to cooperate with examinations and follow-up.

Figure 1 Study schema. UWFFA, ultra-wildfield fluorescein fundus angiography.

4. Positive allergy skin test when conducting UWFFA.
5. Diffuse vascular leakage, macula oedema or any retina lesions demonstrated by UWFFA.
6. History of systemic immunosuppressive therapy within 2 months.
7. History of biological treatment within 2 months.
8. History of triamcinolone acetonide subconjunctival/intraocular injection within 2 months.
9. Current topical GCs eye-drops more than six times per day.
10. History of eye surgery within 3 months.
11. Eye complications that interfere with fundus observation.

Run-in period
Potential candidates meeting up the first two inclusion criteria with active non-infectious anterior uveitis will be given a predesigned regimen as follows to treat the active inflammation: topical prednisolone acetate 6–8 times per day, gradually tapered to two times a day at the fourth week and fully stopped at the eighth week. UWFFA would be scheduled at this time point (table 1). If patients come back 2 weeks later with UWFFA indicating peripheral retinal vascular leakage, further screening tests for potential contraindications of adalimumab and baseline

Table 1 Events or assessments for each follow-up visit

Events or assesments	Time (week)									
	−4	−2	0	2	4	8	12	16	20	24
Demographic information collection*			×							
Review of HPI† and PMI†	×									
Review of current mediation	×	×	×	×	×	×	×	×	×	×
Complete ocular exam‡	×	×	×	×	×	×	×	×	×	×
UWFFA†	×						×			×
Baseline uveitis assessment§		×								
Screening test for recruiment¶		×								
Assessment of eligibility criteria			×							
Written informed consent			×							
Randomisation and start of intervention			×							
Monthly surveillance tests**					×	×	×	×	×	×
Adverse events documentation				×	×	×	×	×	×	×

*Demographic information include patients' age, sex, city of residency, contact information.
†HPI: history of present illness
‡Complete ocular exam includes best-corrected visual acuity, intraocular pressure, cornea, slit lamp evaluation of the cornea, fresh keratic precipitates, anterior chamber cells, vitreous cells and funduscopy to evaluate the optic nerve and the retina.
§Baseline uveitis assessment include complete blood count, urinalysis, antinuclear antibodies, HLA-B27, rheumatoid factor, TNF-α, IL6, erythrocyte sedimentation rate (ESR), C reactive protein (CRP).
¶Screening test for recruitment include liver functions, renal functions, hepatitis B virus, hepatitis C virus, and blood T-SPOT.TB, and chest X-ray.
**Monthly surveillance tests include complete blood count, liver functions, renal functions, TNF-α, interleukin 6, ESR, CRP.
PMI, past medical history; UWFFA, ultra-wildfield fluorescein fundus angiography.

evaluation will be performed, including complete blood count, urinalysis, liver functions, renal functions, hepatitis B virus, hepatitis C virus and blood T-SPOT.TB, antinuclear antibodies, HLA-B27, rheumatoid factor, TNF-α, interleukin 6 (IL6), erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and chest X-ray (table 1). After 1 month of treatment, patients whose active anterior chamber inflammation get controlled and adherent to follow-up will be re-evaluated for eligibility according to the inclusion and exclusion criteria. Potential participants will be introduced the details of this trial. Once the informed consent is signed, eligible patients will proceed to randomisation and demographic information will be collected at the same time (table 1).

Randomisation
Recruited patients will be randomised into the adalimumab group and methotrexate group based on computer-generated random sequence with R package 'experiment',[9] without permuted block or stratification. The random sequence will be kept by an investigator. Allocation concealment will be performed by keeping the random sequence separately from the clinicians who are responsible for the recruitment. Treatment regimen will be allocated after the recruitment through a telegraphone call to the investigator who keeps the random sequence. The visit when the randomisation is performed will be defined as week 0.

Masking
Due to practical issues, masking to the patients is hard to be carried out in this study. The patients' treatment group will be hidden from the clinician who evaluates the patients for each follow-up to avoid assessment bias. The data analysts will be masked to avoid conformation bias.

Intervention
From week 0, patients in the adalimumab group will be administered adalimumab subcutaneously 40 mg every 2 weeks, and patients in the methotrexate group will be given methotrexate 10 mg orally once a week, with folic acid given 0.4 mg on the following day. Topical prednisolone acetate that starts from the run-in period will be gradually reduced and ultimately stopped by week four after randomisation.

Rescue plan
If any inflammatory flare happens, patients will be restarted on topical prednisolone acetate. In addition, patients in the adalimumab group will be given additional oral methotrexate 10 mg once a week, with folic acid 0.4 mg on the following day. Patients in the methotrexate group will be treated with additional adalimumab 40 mg every 2 weeks. Patients will still be followed up in the trial for disease monitoring. If the inflammation worsens again under methotrexate plus adalimumab, other systemic immunosuppressive therapy will be considered.
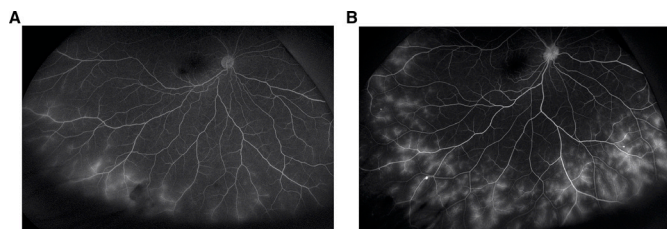
Figure 2 Demonstration of limited (A) and diffuse (B) vascular leakage.

Follow-up plan

During the run-in period and the first months after randomisation, patients will be followed up every 2 weeks. After that, patients will be followed up every month until the end of the study. For each visit, best-corrected visual acuity (BCVA), intraocular pressure, inflammatory parameters including fresh keratic precipitates, anterior chamber cells, vitreous cells will be examined. Funduscopy will be done to evaluate the optic nerve and the retina. The side effects of the therapy will be recorded. Complete blood count, liver functions, renal functions, TNF-α, IL6, ESR, CRP will be performed every month after randomisation. UWFFA will be performed at the 3 months and 6 months visit (table 1). Patients will be followed up by the same ophthalmologist in the uveitis clinic. He/she will also take care of the appointment arrangement for the next visit and record the data collected on the appropriate case report form (CRF). An allowance of −10 days or+10 days will be allowed for monthly visits. Should unscheduled visits be required for any reason, they would be recorded on the 'unscheduled visit' CRF. Lost to follow-up is defined as inability to collect the required data for more than 6 weeks. Should the patient not be able to come to the appointment due to quarantine policies under COVID-19, follow-up visit at their local hospital would be suggested and arranged. Competing risk event include any ocular or systemic condition unrelated to uveitis, such as unexpected ocular trauma, rhegmatogenous retinal detachment, or other unexpected accidents that prevent the primary outcome assessment.

OUTCOME VARIABLES

Primary endpoint: Uveitis flare within the 6 months follow-up.

▶ Uveitis flare is defined as anterior chamber cell count grading increased from 0 to 1.
  – Anterior chamber cell grade will be recorded according to standardisation of uveitis nomenclature (SUN) criteria.[10]
  – Anterior chamber cell grade will be measured by a fixed slit lamp (TOPCON, Tokyo, Japan)
  Secondary endpoints:
▶ BCVA at the 6-month follow-up visit.
  – BCVA will be measured by a standard logarithmic visual acuity chart (GB11533-2011).

▶ Inflammatory parameters including fresh keratic precipitates, vitreous cells at the 6-month follow-up visit.
  – Fresh keratic precipitates will be recorded in a dichotomous method.
  – The slit lamp (TOPCON, Tokyo, Japan) will be pushed forward to the vitreous to observe vitreous cells. The grading method was the same as the anterior chamber cell grading described by SUN
▶ Score of peripheral retinal vascular leakage on UWFFA at the 6-month follow-up visit.
  – Retinal vascular leakage will be quantified based on the method developed by the Angiography Scoring for Uveitis Working Group, in which vascular leakage in the posterior pole and in each peripheral quadrant was scored 1 if limited and scored 2 if diffuse, as demonstrated by figure 2. Total maximum score is 8 since vascular leakage in the posterior pole will be excluded in this study.
  – UWFFA will be performed by Optos California(Optos, USA).
▶ Adverse events
  – Adverse events include local redness around the injection site, mild upper respiratory symptoms, gastrointestinal symptoms, the infectious events and laboratory parameter abnormalities.

Sample size calculation

The null hypothesis is that adalimumab and methotrexate perform equally in preventing the inflammatory flare of uveitis in children with non-infectious anterior uveitis. To detect a relative reduction of 30% between a presumed failure risk of 10% in the adalimumab group and 45% in the methotrexate group, with 80% power at 5% significance and 1:1 randomisation, a total of 48 patients will be required. Taking the lost to follow-up rate of 5% into consideration, the sample size is increased to 50 patients.

A pilot study was done in our centre for paediatric non-infectious uveitis with peripheral retina vascular leakage,[11] in which among 20 children who had active anterior uveitis treated with adalimumab, no patients had inflammatory flare within 6 months follow-up. However, in that retrospective study, topical GCs and systemic immunomodulatory therapy were adjusted and not unified. Thus, we propose a maximum of 10% inflammatory flare rate in the adalimumab in this study. The inflammatory flare rate of 45% in the methotrexate group is estimated from an RCT published in NEJM,[6] in which JIA-associated paediatric uveitis was treated with methotrexate plus placebo in the control group and had treatment failure rate of 45% at the 6 months follow-up according to its the Kaplan-Meirer curve. We estimate that lost to follow-up will be approximately less than 5% based on the severe nature of this disease potentially causing vision loss, and the clinical experience of our study centre.

Statistical analysis

For the primary endpoint, χ^2 or Fisher's exact test will be performed to compare the flare rate between the adalimumab group and methotrexate group. For secondary endpoints, BCVA will be transformed to the logarithm of the minimum angle of resolution (log MAR) for data analysis. Student's t-test or Wilcoxon test will be used to compare the BCVA, vascular leakage scores between groups depending on the homogeneity of variance. Wilcoxon test will be performed to compare the inflammatory parameters. Adverse events will be presented in a descriptive way. The two-sided test will be used for all statistical analysis, and $p < 0.05$ is statistically significant. Main analysis will be conducted using complete case dataset while sensitivity analysis will be conducted using multiple imputation if there were any missing data.

Patient and public involvement

No patient or member of the public was involved in either the design, or conduct, or reporting, or dissemination plans of this research.

Trial status

At the time of manuscript submission, this trial had recruited nine patients.

Ethics and dissemination

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital, Beijing, China (Approved protocol V3, dated 27 July 2021. Approval number 25-ZS-3062) and has been registered on ClinicalTrials.gov. Written informed consent will be collected from every patient and their guardians prior to study participation. The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication.

DISCUSSION

With the advancement in biologic studies, the prognosis of uveitis becomes much better if patients could be treated properly and timely. The aim of uveitis management is shifting from a short-term inflammatory control to long-term disease quiescence, as well as minimisation of complications and side effects of medical therapies. In previous studies, much effort has been paid to investigate the efficacy of adalimumab in serious and refractory uveitis, such as Bechet's uveitis, posterior or pan-uveitis and JIA-associated uveitis. In this study, we designed an RCT that focuses on relatively mild chronic anterior uveitis, but with peripheral retinal vascular leakage that is usually a sign of chronic inflammation.

Peripheral retinal vascular leakage is a common sign of chronic inflammation, Yang *et al* have showed that almost 80% of patients with paediatric idiopathic uveitis show manifestations of retinal vasculitis, which is associated with a lower probability of inflammation control resulting in a worse visual prognosis.[12] There were also studies showing that peripheral vascular leakage was correlated with active inflammation, often led to treatment augmentation,[13 14] and might be a more objective parameter to standardise disease monitoring.[15 16] In our previous clinical observation, children with anterior uveitis usually have a good response to topical GCs but still have recurrent or chronic course of disease. The long-term topical GCs usage and the recurrent intraocular inflammation cause complications such as cataract formation, band keratopathy and high intraocular pressure, resulting in frequent hospital visits, multiple surgeries that affect the physical, mental, social health and overall development of adolescents. When we performed UWFFA on these patients, most of them presented with peripheral retinal vascular leakage. Thus, a pilot study was finished to assess the efficacy of adalimumab to induce the remission of peripheral retinal vascular leakage and anterior chamber inflammation. And the preliminary results were encouraging.[11] However, the aim of uveitis management is to keep patients under disease quiescence with a safe and economical therapy. The superiority of adalimumab over traditional methotrexate therapy is still worth debating.

This study focuses on peripheral retinal vascular leakage, comparing the efficacy and safety of adalimumab and methotrexate to prevent inflammatory flare in paediatric non-infectious anterior uveitis with peripheral retinal vascular leakage, trying to provide a new specific indication for adalimumab to improve the prognosis and quality of life for paediatric uveitis patients. If the superiority of adalimumab could be confirmed by this study, children with this condition could benefit from reduced intraocular inflammation periods and avoid the side effects of traditional therapy such as cataract formation, secondary glaucoma, growth retardation and liver damage. If adalimumab performed less effective than methotrexate, traditional therapy would be suggested for this group of patients for economic efficiency.

Limitation

The main limitation of this protocol is that patients could not be masked to their treatment group as methotrexate and adalimumab are given in different route. Also, the measurement of primary outcome is partial subject. However, as the anterior chamber cell observed by the slip lamp is crucial to measure uveitic flare according to SUN criteria, this limitation could only be minimised by blinding the clinician who measures and documents the data.

Author affiliations

[1]Department of Ophthalmology, Key laboratory of Ocular Fundus Diseases, Peking Union Medical College Hospital, Beijing, China

[2]Medical Research Center, Peking Union Medical College Hospital, Beijing, China

[3]Department of Ophthalmology, Fudan University Eye Ear Nose and Throat Hospital Department of Ophthalmology, Shanghai, China

ORCID iDs
Hang Song http://orcid.org/0000-0002-0234-6801
Yuelun Zhang http://orcid.org/0000-0001-7990-9003

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