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Concise report

# Use of adalimumab in refractory non-infectious childhood chronic uveitis: efficacy in ocular disease—a case cohort interventional study

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## Abstract

**Objective.** To assess the use of adalimumab in the treatment of refractory non-infectious childhood chronic uveitis.

**Methods.** A case cohort interventional study was performed on patients with uveitis, who were treated with adalimumab after failure of treatment with a combination of corticosteroids and another immunosuppressant drug. Main outcome measures were (i) stability of vision, (ii) stability of inflammation and (iii) reduction of immunosuppressive load. Adverse events and reasons for stopping adalimumab were noted.

**Results.** Seventeen patients from a single regional centre were included in the study. Nine patients had previously received an anti-TNF agent, and because of inefficacy, all were changed to adalimumab. At 12 months, fewer patients had visual acuity worse than LogMAR 0.4 (18% vs 32% at baseline). Using standardized uveitis nomenclature criteria, at 3 months, 50% of the patients eyes ($n = 32$) had improved, 16% had stable inflammation and 3% had worsened, whereas 31% were maintained with no anterior chamber cells. Six patients required courses of oral steroids for uveitis. Seven patients received intra- or periocular injections of steroids. Adalimumab treatment was interrupted in one patient because of varicella zoster infection. It was stopped in three patients. Seven (41%) patients reported injection site reactions.

**Conclusion.** In this group of children with refractory uveitis, use of adalimumab was associated with improvement in visual acuity and improving or stable ocular inflammation. However, it did not completely obviate the need for systemic or periocular steroid treatment. Prospective randomized controlled trials are required to help determine which subset of patients may benefit from adalimumab and the duration of treatment.

**Key words:** adalimumab, anti-TNF treatment, juvenile idiopathic arthritis, uveitis.

## Introduction

Chronic non-infectious uveitis in childhood is relatively uncommon, but it is a potentially sight-threatening condition with long-term morbidity associated with the condition itself and its treatments [1–4]. This highlights the importance of early control of inflammation and avoidance of long-term use of high-dose corticosteroids by using steroid-sparing agents.

Adalimumab is a fully humanized recombinant monoclonal IgG-1 antibody against TNF-α that binds soluble and transmembrane cytokine, thus inhibiting its activity. There have been several retrospective observational studies of series of children with uveitis treated with adalimumab and a multinational e-mail survey of doctors caring for this patient group [5–9]. The studies included 3–20 children treated with adalimumab for uveitis, with variable duration of follow-up. They all concluded that adalimumab is effective in some children with uveitis. However, they did not define clear reasons for the use of adalimumab and did not use accepted standardization of uveitis nomenclature (SUN), making direct comparison difficult.

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In this article we describe prospectively collected outcome data from our cohort of children with refractory non-infectious chronic uveitis treated with adalimumab.

## Materials and methods

A review of data recorded contemporaneously on specifically designed proforma sheets, which incorporated SUN criteria, was performed on patients with refractory chronic uveitis treated with adalimumab in a combined paediatric rheumatology and ophthalmology clinic at a single centre in UK. Patients were included if they had been diagnosed with non-infectious uveitis and were being treated with adalimumab, with at least 6 months follow-up since January 2008. Data collection end points were as follows: (i) cessation of adalimumab for any reason, (ii) loss to follow-up or (iii) continued adalimumab therapy at the time data collection stopped in February 2011.

In patients with JIA, the diagnosis was according to ILAR criteria [10]. Uveitis was diagnosed and documented according to SUN criteria. The decision to start adalimumab was made based on uncontrolled or worsening joint disease or uveitis despite treatment with corticosteroids and at least one other immunosuppressive agent. Uncontrolled uveitis was defined as persistent inflammation of SUN grade 1+ or more anterior chamber cells or co-morbid disease with cystoid macular oedema, vitritis, raised intraocular pressure or development of cataract. Subcutaneous adalimumab was given every other week at a dose of 20 mg or 40 mg depending on the patient's weight.

The proforma sheets of the enrolled patients were reviewed after obtaining consent from their parents or guardians. Patient demographics, diagnosis and previous or ongoing therapies were recorded. The following baseline ophthalmological data were noted: visual acuity (VA), anterior chamber cells, vitreous haze, cystoid macular oedema, intraocular pressure, presence of cataracts or band keratopathy. Snellen VA was documented and converted to LogMAR vision for analysis [11]. Ocular inflammation was assessed using the SUN grading system [11]. The number of active joints was also noted.

Patients were seen in combined regional paediatric rheumatology and ophthalmology clinics at least every 3 months. At each visit, joint and uveitis activity were assessed and topical and systemic medications were recorded. Patient's compliance with therapy and any infections or adverse events were noted at each attendance by uveitis and paediatric rheumatology specialist nurses.

To overcome potential bias, particularly with regard to VA [12], we summarized the proportion of patients with VA worse than LogMAR 0.4 at 12 months compared with before starting adalimumab. Following SUN recommendations, improved uveitis activity was defined as either a two-step decrease in the level of inflammation or a decrease to grade 0, and worsening activity was defined as either a two-step increase in the level of inflammation or an increase to grade 4. Data are reported for each eye separately.

Frequency of events is reported as incidence rates per eye-year (EY) or per patient-year (PY) and is calculated as follows: event rate/EY = $\Sigma$(number of events)/$\Sigma$[time (since starting adalimumab) to event or data collection end point]. The probabilities of events occurring after adalimumab was started are presented as survival curves, using the product-limit method of Kaplan and Meier [13]. These analyses were done using GraphPad Prism (version 4.0 for Windows; GraphPad Software, San Diego, CA, USA).

## Results

### Characteristics of study population

Seventeen patients (10 female, 59%; median age 10 years, median duration of uveitis 4 years) met inclusion criteria for this study. Their diagnoses and demographic characteristics are summarized in Table 1. The drug was started for control of uveitis in seven patients and for control of uveitis and arthritis in 10 patients. Previous treatments (including anti-TNF agents in nine patients), concomitant medications and ophthalmological data at baseline and at 3 and 12 months are shown in Table 1. The patients were seen at ~3-month intervals, with a median follow-up time of 24 months (range 6–36 months).

### VA and uveitis activity

Median baseline VA was logMAR 0.1. Before starting adalimumab, 34% of eyes ($n = 32$) had VA of logMAR 0.4 or worse, and in 2 of 32 eyes (6%) VA was 1.0 or worse. At 3 months, this was 29% and 6%, respectively; at 12 months it was 18% and 7%, respectively ($n = 28$).

Twenty of 32 eyes (62.5%) showed inflammation and 12 (37.5%) eyes showed no inflammation at baseline. Of the latter, 10 remained inactive throughout follow-up. At 3 months after starting adalimumab, 80% of eyes ($n = 20$) had improved vision and 20% had stable inflammation. Among the same 20 eyes, 19 subsequently had no inflammation for at least 3 months between starting adalimumab and the census date. Resolution of anterior chamber activity with respect to time after starting adalimumab is presented in Fig. 1. The rate of maintenance or drug-induced remission among eyes was 3.4/EY. The equivalent for patients was 2.5/PY. For the eyes with no inflammatory activity at baseline, the relapse rate was 0.011/EY. Of the 19 eyes achieving remission after starting adalimumab, 6 (5 JIA-associated, 1 sarcoidosis) subsequently relapsed, giving a rate of 0.22/EY.

Six of 28 eyes (21%) showed vitreous haze at baseline. This had improved in five of the six eyes by 9 months and was static in one (with sarcoidosis). Eight eyes developed vitreous haze [binocular indirect ophthalmoscopy (BIO) score 1 or 2] during follow-up. Seven of 30 eyes (23%) had cystoid macular oedema at baseline, which had improved in five eyes (three JIA-associated, two idiopathic panuveitis).

### Adalimumab doses and other medications

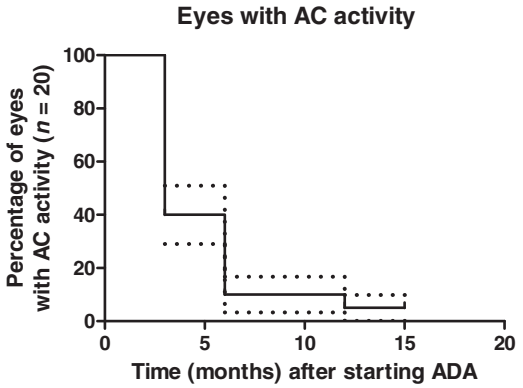
Adalimumab was administered subcutaneously every fortnight (20 mg or 40 mg depending on patient's

**Table 1** Patient characteristics, previous treatments, clinical features before and after treatment with adalimumab

| Gender | Age (years) | Diagnosis | Duration of uveitis when ADA started (years) | Reason for ADA | Age when ADA started (years) | MTX | Previous treatment | ADA dose | Medications | | | Eye | Visual acuity | | | Anterior chamber cells | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 0 m | 3 m | 12 m | | 0 m | 3 m | 12 m | 0 m | 3 m | 12 m |
| M | 5 | Oligoarticular JIA | 0 | Uveitis and arthritis | 3 | 5 mg p.o. | ETA | 20 mg | TS, MTX 10, Pred 1 mg/kg | TS, MTX 10, orbital floor triamcinolone | TS, MTX 10 | RE | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | | | | | | | LE | 0.8 | 0.8 | 0.18 | 1 | 0 | 1 |
| F | 9 | Oligoarticular JIA, ANA +ve | 5 | Uveitis | 8 | Unable to tolerate | ETA | 20 mg | TS | TS | TS | RE | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | | | | | | | LE | 0 | 0 | 0 | 3 | 1 | 0 |
| F | 12 | Oligoarticular JIA | 5 | Uveitis and arthritis | 10 | Unable to tolerate | MMF, INF | 40 mg | TS, MMF 500 | MMF 500 | TS, Pred 30 mg daily | RE | 0 | 0 | 0 | 0 | 0 | 1 |
| | | | | | | | | | | | | LE | −0.1 | 0 | 0 | 0 | 0 | 0 |
| F | 17 | Oligoarticular JIA, ANA +ve | 4 | Uveitis and arthritis | 15 | 15 mg s.c. | MMF | 40 mg | MTX 15, MMF 1000 | MTX 15, MMF 1000 | TS, MTX 15, MMF 1000 | RE | −0.1 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | | | | | | | LE | 0 | 0.18 | 0.18 | 1 | 0 | 2 |
| F | 9 | Polyarticular JIA | 1 | Uveitis and arthritis | 6 | 12.5 mg s.c. | INF | 20 mg | TS, MTX 12.5, INF | TS, MTX 12.5 | TS, MTX 12.5, MMF 250, Pred 5 mg daily | RE | 0.3 | 0.3 | 0.18 | 1 | 0 | 1 |
| | | | | | | | | | | | | LE | 0.5 | 0.5 | 0.3 | 2 | 0 | 3 |
| F | 9 | Polyarticular JIA, ANA +ve | 1 | Uveitis | 6 | 10 mg p.o. | MMF, INF | 20 mg | TS, MTX 10, MMF 480 | TS, MTX 10, MMF 480 | TS, MMF 480 | RE | 0.18 | 0.3 | 0.3 | 1 | 1 | 0 |
| | | | | | | | | | | | | LE | 0.8 | 0.6 | 0.18 | 3 | 1 | 0 |
| M | 12 | Polyarticular JIA, ANA +ve | 3 | Uveitis and arthritis | 9 | 10 mg p.o. | MMF, INF | Started 20 mg then 40 mg | MTX 10, MMF 500 | TS, MTX 10, MMF 500 | MMF 500 | RE | 0 | 0 | 0.18 | 2 | 1 | 0 |
| | | | | | | | | | | | | LE | 0 | 0 | 0 | 1 | 1 | 0 |
| F | 12 | Polyarticular JIA, ANA +ve | 8 | Uveitis | 11 | 20 mg s.c. | MMF, Pred | 40 mg | MTX 20, Pred 1 mg/kg | TS, MTX 20, R trab | TS, MTX 20 | RE | 0.8 | 0.5 | 0.5 | 2 | 0 | 0 |
| | | | | | | | | | | | | LE | −0.1 | −0.1 | −0.1 | 0 | 0 | 0 |
| M | 12 | Psoriatic JIA | 3 | Uveitis and arthritis | 10 | 17.5 mg p.o. | MMF | 40 mg | TS, MTX 17.5, MMF 500 | TS, MTX 17.5, MMF 500 | TS, MTX 20, MMF 1000 | RE | 0 | −0.1 | −0.1 | 3 | 1 | 0.5 |
| | | | | | | | | | | | | LE | 0.5 | 0.8 | 1.08 | 3 | 1 | 0 |
| F | 12 | Psoriatic JIA | 5 | Uveitis and arthritis | 10 | 7.5 mg s.c. | INF, previous trab BE | 40 mg | TS, MTX 7.5, INF | Nil | TS, MTX 7.5 | RE | 0.5 | 0.18 | 0.18 | 1 | 0 | 0 |
| | | | | | | | | | | | | LE | 0.3 | 0 | 0.6 | 0 | 0 | 0 |
| M | 17 | Psoriatic JIA | 10 | Uveitis and arthritis | 15 | 20 mg s.c. | MMF | 40 mg | TS, MTX 20, MMF 1000 | TS, MTX 20, MMF 1000 | TS, MTX 20, MMF 1000 | RE | 0 | 0.18 | 0 | 1 | 0 | 0 |
| | | | | | | | | | | | | LE | 0.5 | 0.18 | 0.3 | 1 | 0 | 0 |
| F | 18 | Psoriatic JIA | 5 | Uveitis | 17 | 15 mg p.o. | INF | 40 mg | MTX 15 | TS, MTX 20 | MTX 20, Intravit steroid | RE | 0 | 0 | 0.18 | 0 | n/a | 0 |
| | | | | | | | | | | | | LE | −0.1 | −0.1 | −0.1 | 0 | n/a | 0 |
| M | 15 | Sarcoidosis | 4 | Uveitis and arthritis | 12 | 25 mg s.c. | Pred | Started 30 mg then 40 mg | MTX 25, Pred 0.5 mg/kg | MTX 25 | MTX 20, MMF 800, hydrocort | RE | 0.8 | 0.8 | 0.8 | 2 | 0 | n/a |
| | | | | | | | | | | | | LE | 0 | 0 | 0 | 1 | 0 | n/a |
| M | 10 | Blau syndrome, refractory granuloma-tous uveitis | 2 | Uveitis and arthritis | 8 | 10 mg p.o. | ETA, anakinra | 20 mg | TS, MTX 10 | TS, MTX 10 | n/a | RE | 0 | 0 | n/a | n/a | 0 | n/a |
| | | | | | | | | | | | | LE | 0 | 0.3 | n/a | n/a | 1 | n/a |
| F | 20 | Blau syndrome | 14 | Uveitis | 19 | 20 mg p.o. | Pred | 40 mg | TS, MTX 20, Pred 5 mg | TS, MTX 20, Pred 5 mg | n/a | RE | 0.3 | 0.3 | n/a | 2 | 1 | n/a |
| | | | | | | | | | | | | LE | 1 | 1 | n/a | 0 | 0 | n/a |
| M | 16 | Panuveitis with scleritis, HLA-B5 +ve | 3 | Uveitis | 15 | 12.5 mg p.o. | Pred, ST steroid | 40 mg | MTX 12.5 | TS, MTX 10, Pred 5 mg | TS, MTX 10, Pred 5 mg | RE | 2.3 | 1 | 2.6 | 0 | 2 | n/a |
| | | | | | | | | | | | | LE | 0.18 | 0.88 | −0.18 | 0 | 0 | n/a |
| F | 17 | Idiopathic panuveitis | 3 | Uveitis | 15 | 15 mg p.o. | MMF, Pred | 40 mg | MTX 15, MMF 500, Pred 10 mg | MMF 500 | MMF 500 | RE | 0.5 | 0.6 | 0.8 | 1 | 0 | 0 |
| | | | | | | | | | | | | LE | 0.3 | 0.1 | 0.3 | 2 | 0 | 0 |

MMF dose in milligrams, twice daily; MTX dose in milligrams, once weekly. ADA: adalimumab; BE: both eyes; ETA: etanercept; INF: infliximab; LE: left eye; n/a: data not available; m: month; Pred: oral prednisolone; RE: right eye; ST: sub-Tenon's capsule injection; trab: trabeculectomy; TS: topical steroids.

FIG. 1 Time to resolution of anterior chamber cell activity in eyes of patients taking adalimumab for chronic non-infectious uveitis (95% CI).




Number of eyes at each time point (months): 20 (0), 20 (3), 17 (6), 11 (9), 17 (12), 10 (15), 13 (18), 6 (21) and 14 (24).

weight). Two patients had the dose increased from 20 mg to 40 mg: one because of inadequate control of arthritis and another because their weight was >30 kg. Fifteen of 17 patients were on MTX from baseline. One patient commenced MTX after 15 months on adalimumab because of worsening uveitis and arthritis. Eight patients were taking MMF at the time adalimumab was started and two patients commenced MMF at 12 months after starting adalimumab because of worsening uveitis and non-improving uveitis. The rate of introduction of MMF was 0.2/PY.

Six patients were receiving oral prednisolone at baseline, which was tapered during the first 3 months in four patients. One patient continued oral steroids during the study period. Another stopped steroids by 6 months but was recommenced at 9 months because of uveitis, and this was maintained. Three other patients received oral steroids.

Thirteen patients were receiving steroid eye drops at baseline. Of these, four were able to stop the topical drops, giving a rate of cessation of 0.26/PY. Two patients restarted topical steroid drops for uveitis.

Eight patients were able to reduce the dose of topical steroid eye drops during the first 12 months on adalimumab (1.1/PY). Three patients did not achieve full control of uveitis and had fluctuating doses of topical steroids during the follow-up period. Seven patients received intra- or periocular injections of steroid while on adalimumab, one patient having three intravitreal injections.

### Ophthalmic complications

The intraocular pressure was elevated (>24 mm Hg) in 13% of eyes at baseline. In these patients, one eye had a trabeculectomy performed within 3 months of starting adalimumab and required three agents to control intraocular pressure during 18 months of follow-up. The other patient, with two affected eyes, had trabeculectomies performed at 9 months from baseline. One patient developed glaucoma in both eyes after 18 months on adalimumab that required topical therapy and bilateral trabeculectomy.

Of 32 eyes at baseline, 5 were pseudophakic. In the remaining 27 eyes, 6 had a cataract at baseline and 2 developed cataract during follow-up. Two patients had cataract surgery and intraocular lens insertion during the follow-up period.

### Arthritis activity

Five patients had active joints at baseline, which improved in all over 12 months. However, two patients subsequently had intra-articular steroid injections. Four other patients who had no active joints at baseline required intra-articular steroids for flares of arthritis.

### Adverse events and discontinuation of adalimumab

The total adalimumab exposure was 28.75 PY. There were no serious side effects or adverse events associated with adalimumab. Seven patients (41%) reported stinging and injection site reactions, in one case lasting up to a week.

Two patients omitted a single dose because of intercurrent infections, including varicella zoster. One teenage patient was non-compliant for 7 weeks but subsequently restarted the medication.

The parents of one patient decided to stop adalimumab because of multiple courses of antibiotic medications for chest infections. One patient developed severe headaches within 3 months and had features of raised intracranial pressure and concerns about tuberculous meningitis, therefore adalimumab and MTX were stopped. However, there were no tuberculosis contacts, and tests of cerebrospinal fluid, Mantoux and quantitative $\gamma$-interferon assays were all negative. After 24 months of treatment, one patient's arthritis and uveitis were inadequately controlled and a switch from adalimumab to abatacept was made.

## Discussion

We have presented a series of 17 children with non-infectious chronic uveitis who had not achieved full control with topical corticosteroids, MTX and, in 9 cases, other anti-TNF agents, but who then subsequently showed improvement in VA and intra-ocular inflammation with adalimumab. The rate of maintenance or drug-induced remission among eyes was 3.4/EY. Anterior chamber inflammation improved in 50% of eyes after 3 months on adalimumab. In comparison, Tynjälä *et al*. [5], who also used the SUN criteria to determine outcome measures, found improvement in 20% of eyes ($n = 40$). Direct comparison with other studies [6–9] is not possible because of different inclusion criteria, varying definitions of improvement and use of outcomes at the most recent follow-up. As Jabs noted [12], studies with variable follow-up do not take into account the effect of time. We have overcome this by making comparisons at fixed time points after starting adalimumab and using rates of event occurrence per PY or per EY captured on standardized proformas.

It is clear that adalimumab did not completely obviate the need for steroids, with 29% patients having oral prednisolone, 41% receiving intra- or periocular steroid injections and 35% having intra-articular steroids. However, 29% of patients were able to stop topical steroids for a period (event rate 0.26/PY), and in 71% it was possible to wean the dose (event rate 1.1/PY). This is of significance because of the morbidity associated with topical corticosteroids [3, 4, 14].

This study included 12 patients with JIA, of whom 6 were previously treated with infliximab and 2 with etanercept. There was improvement in intraocular inflammation in all eight patients who had previously received anti-TNF treatment. This supports findings from other studies in which there was a secondary failure of a first biologic agent but effectiveness of a different anti-TNF [15]. This study represented a 28.75 PY experience of adalimumab in the paediatric population. During that time there were no serious adverse events.

There are several limitations of this study and any subsequent conclusions made. First, the relatively small sample size and heterogeneity of the cohort; secondly, although decisions to start adalimumab followed our standardized practice, there are no consensus guidelines; and thirdly, there was no comparative control group. The results do support the current randomized, double-blind, placebo-controlled and multicentre trial of adalimumab in combination with MTX in patients with active refractory uveitis associated with JIA [the Clinical Effectiveness, Safety and Cost Effectiveness of Adalimumab in Combination with Methotrexate for the Treatment of Juvenile Idiopathic Arthritis Associated Uveitis (SYCAMORE) trial] [16].

**Rheumatology key messages**

- Adalimumab may be helpful in MTX-refractory childhood uveitis.
- Biologic therapy modifies the outcome of childhood uveitis.
- Preliminary evidence supports a trial of adalimumab in childhood uveitis.

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