

Adalimumab for childhood onset uveitis

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Juvenile idiopathic arthritis (JIA)-associated uveitis is the most common cause of paediatric uveitis and is associated with significant visual morbidity.¹ Despite considerable improvements in the treatment of JIA, most trials of biological agents in JIA excluded children with uveitis for methodological reasons. This has meant a limited evidence base and availability of biological therapies for paediatric uveitis. The ADJUVITE study² published in this journal and the recently published SYCAMORE study³ both provide much needed evidence for use of biologics in children with uveitis.

The ADJUVITE study² randomised 32 patients with childhood onset anterior uveitis and an inadequate response to topical steroid and methotrexate (MTX), based on a laser flare photometry (LFP) reading of ≥ 30 photon units/ms, to fortnightly adalimumab or placebo. The primary outcome was response to treatment at the end of month 2, defined as a reduction of at least 30% of ocular inflammation on LFP with no worsening of anterior chamber cells or flare according to Standardised Uveitis Nomenclature (SUN) criteria.⁴ In the adalimumab group, 9/16 patients had a 30% reduction in flare on LFP compared with 3/15 in the placebo group, which was statistically significant, but as the authors acknowledge should be interpreted with some caution as the CI included 1. There was no significant reduction in anterior chamber cell scores.

This small study, following on from the SYCAMORE trial,³ which was stopped early due to evidence of efficacy of adalimumab for JIA-associated uveitis, provides further support for the use of adalimumab in childhood uveitis.

However, there are striking differences between the ADJUVITE and SYCAMORE studies. SYCAMORE recruited 90 children with JIA-associated uveitis who had failed treatment with topical or systemic glucocorticoids and MTX and had active uveitis with $\geq 1+$ anterior chamber cells based on the SUN criteria. The primary

outcome of SYCAMORE was time to treatment failure based on the SUN anterior chamber cell grading score. The ADJUVITE participants had lower cellular activity at baseline than those in the SYCAMORE study; indeed, 15 patients (48%) in ADJUVITE with a cell count of 0–0.5+ would not have been eligible for entry to the SYCAMORE study. Despite the lower cell counts, eyes in the ADJUVITE study had greater morbidity with 76% of eyes having posterior synechiae compared with 27% in the SYCAMORE study.

These trials leave us with important questions to answer over which children should be offered adalimumab, how we should monitor inflammatory activity in clinical practice and what we should measure in clinical trials in paediatric uveitis.

One of the limitations of the SYCAMORE study was the exclusion of children with idiopathic uveitis, which ADJUVITE does try to address. Although only two children with idiopathic uveitis are included in the study, it is important to acknowledge that idiopathic chronic anterior uveitis in children has a similar course to JIA-associated uveitis.⁵ The trial results cannot be generalised to posterior segment uveitis, where evidence for biological treatment remains limited.

Grading of uveitis activity on slit-lamp examination was standardised by the SUN working group in 2005 with anterior flare and cells graded on a scale of 0–4 (4). Flare is the cloudy appearance of aqueous humour due to accumulation of protein and the anterior chamber cell score is based on the number of cells seen in a 1×1 mm slit-lamp beam. While the anterior chamber cell grading score is used routinely in clinical practice to determine disease activity and to make management decisions, the anterior chamber flare score is less discriminatory with clustering at the lower end of the score range.³ Laser flare photometry offers a more objective reproducible measure of flare with a greater range of readings, but requires specialist equipment and may be unreliable in certain situations such as a shallow anterior chamber or an eye with a mature cataract.⁶

Ocular inflammation at baseline, whether measured by aqueous flare $\geq 1+$,

LFP ≥ 20 or anterior chamber cells $\geq 1+$, has been shown to be predictive of vision loss and ocular complications in childhood uveitis,^{7–9} although flare at presentation tends to be a stronger predictor of visual loss.^{10 11} Anterior chamber cells during follow-up of ≥ 0.5 to $\geq 1+$ are associated with loss of visual acuity in eyes with JIA uveitis^{7 10} with a progressive increase in risk of sight loss as cell counts increase.¹⁰ Conversely, low SUN cell counts and flare on LFP at baseline and during follow-up is associated with lower rates of complications.^{9 11} However, cell counts and LFP readings do not always correlate and children may have high flare readings but low cell counts, as was seen in the ADJUVITE study, and the reverse has also been reported¹¹ (see table 1).

ADJUVITE has shown that flare may reduce with adalimumab treatment in patients with low cellular activity, but there remains uncertainty over whether anterior chamber flare is always representative of active inflammation and if treatment of flare alters the outcome of the disease.¹²

The failure of ADJUVITE to show a significant improvement in cellular activity is likely to be due to the low cellular activity at baseline and the short interval to the primary end point at only 2 months. In most trials of biological agents in JIA, it has taken 3–4 months to show a clinical response to the treatment.^{13 14} It is very likely that chronic anterior uveitis, like arthritis, will need therapy for at least 3 months before one could state that the agent is not effective.

Adalimumab is costly with the potential for adverse events³ and unknown long-term risks. The short follow-up period in ADJUVITE limits conclusions on the safety of adalimumab. However, both ADJUVITE and SYCAMORE³ have shown that adalimumab is well tolerated in children with uveitis, and more children were withdrawn from SYCAMORE for MTX intolerance than for problems related to adalimumab. This is important as emotional reactions to treatment have a significant impact on quality of life in JIA-associated uveitis.¹⁵ Duration of therapy is also an important consideration in children, and we need longer term outcomes to determine the optimal time to intervene and withdraw biological therapy in childhood uveitis.

ADJUVITE and SYCAMORE have approached the same research question in very different ways, despite broadly following published proposed outcome measures for clinical trials in JIA-associated uveitis.¹⁶ We should look to

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Table 1 Measurement of anterior chamber inflammation in uveitis

SUN anterior chamber cells	Laser flare photometry
No additional equipment	Laser flare photometer and trained operator
Some patient cooperation required	Greater patient cooperation required
Sign of inflammation	Sign of inflammation±damage
Semiquantitative, limited range of measurements, less reproducible	Quantitative, fully objective, greater range of measurements, reproducible
Dependent on experience	Measurements affected by time of day, age, mydriasis, cataract ⁶
Cells ≥0.5–1+ associated with vision loss and ocular complications ^{7,10} and <1+ cells with reduced complications ⁹	Elevated flare associated with vision loss and ocular complications ¹² and flare <20 photon units/ms with reduced complications ¹¹
Not validated for paediatric uveitis but widely used in clinical practice and in adult uveitis trials ^{17,18}	Not validated for paediatric uveitis. Limited use in clinical practice and research

SUN, Standardised Uveitis Nomenclature.

validating scores of inflammation for children and forming a consensus on the management of paediatric uveitis trials for the future.

The advent of several new agents (biologics and JAK inhibitors) does bring the prospect of more trials in children with uveitis. It is important that future trials include both JIA associated and idiopathic uveitis children in studies. ADJUVITE and SYCAMORE have firmly provided the evidence for adalimumab in MTX-refractory uveitis. This would make placebo-controlled or randomised placebo phase design studies less feasible or palatable for patients and clinicians. We believe adaptive designs involving small numbers of patients in open-label or comparator studies is the 'need of hour' to achieve better outcomes in the management of children with refractory uveitis.

Correction notice This article has been corrected since it published Online First. In the last line of paragraph 4, 'APTITUDE' was changed to 'SYCAMORE' in the sentence "Despite the lower cell counts, eyes in the ADJUVITE study had greater morbidity with 76% of eyes having posterior synechiae compared with 27% in the SYCAMORE study."

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