



# **Clinical Commissioning Policy: Adalimumab (Humira) and Infliximab (Remicade) as Anti-TNF Alpha Treatment Options for Paediatric Patients with Severe Refractory Uveitis**

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# **Clinical Commissioning Policy: Adalimumab (Humira) and Infliximab (Remicade) as Anti-TNF Alpha Treatment Options for Paediatric Patients with Severe Refractory Uveitis**

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## Policy Statement

NHS England will commission infliximab and adalimumab for uveitis in paediatric patients in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

## Equality Statement

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

## Plain Language Summary

Uveitis is the term used to describe inflammation of any structure within the eye that when very severe may cause visual loss. Uveitis accounts for around 10% of visual impairment registrations.

In children, uveitis is commonly associated with juvenile arthritis where the eyes are affected in a similar way to the joints. Uveitis may occur before the onset of joint inflammation, and some children develop identical eye disease without ever having inflammation of the joints.

In severe cases treatment to try to prevent sight loss requires drugs that suppress immune cells (the white blood cell that protect us from infection and damage to our tissues) These are associated with significant short and long term side effects.

The next step in treatment is the use of a group of drugs known as 'biologics'. These are very specialized and are designed to focus on specific molecules released during inflammation from cells and by doing so suppress inflammation. As a result of basic research and research in models to show how effective biologics are for uveitis, a type of biologic called anti-TNF (either Infliximab or Adalimumab) is now the standard of care for severe cases across the world

Anti TNF agents have superseded alternative drugs to steroids in the treatment of juvenile arthritis, as they have been shown to be more effective and to have fewer side effects. Anti-TNF agents have also been observed to be effective against uveitis when given for the treatment of arthritis.

A randomized controlled trial, the SYCAMORE study is in progress. The SYCAMORE trial is specifically for children who have uveitis associated with juvenile arthritis and compares the efficacy of Adalimumab to placebo.

Children eligible for Adalimumab are:

- Those whose Uveitis and associated juvenile arthritis makes them eligible for and they choose to join the SYCAMORE trial
- Those whose Uveitis makes them eligible for the SYCAMORE trial but who do not have associated juvenile arthritis or uveitis which is too severe to meet the inclusion criteria of SYCAMORE and therefore cannot enter the trial
- Those who exit the SYCAMORE trial as they are not responding to treatment and it is found that they have been receiving a placebo
- Those who exit the SYCAMORE trial at the end of the trial and are found to have been receiving Adalimumab and have responded to it.

This policy sets out the background to treatment of Uveitis, known evidence of how well anti-TNF treatments work, the patient need and care pathways as to how anti-TNF treatments will be used throughout England, so that all patients who need the treatment will be able to benefit from it

## 1. Introduction

Uveitis, or inflammation of the uveal tract, is a term used to describe inflammation inside the eye. It can lead to blindness either through direct damage to the light-sensitive retina, or through secondary complications such as glaucoma. The Standardization of Uveitis Nomenclature (SUN) Working Group reported consensus diagnostic terminology, inflammation grading schema and outcome measures for uveitis in 2005.

### **Predictors of Permanent Visual Impairment in Children with Uveitis**

Permanent visual impairment in children with uveitis is associated with, at first presentation: poor vision (<6/18); high inflammatory activity; uveitis onset before diagnosis of arthritis; <6 month interval between onset of arthritis and onset of uveitis; early onset of disease; long duration of uveitis; macular oedema; dense vitreous opacity; ocular hypotony (low intraocular pressure), and glaucoma (Kotaniemi 2008, Kanski 1997, Kanski 1990, Cabral 1994). The presence of prolonged inflammation following diagnosis, even at a low level (>0.5+) is associated with an increased risk of loss of vision (Thorne 2007).

### **Treatment of Uveitis in Children**

The aim of treatment is to minimise chronic ocular inflammation and thereby reduce the risks of ocular complications leading to visual impairment. Induction of early remission of inflammation is felt to be important in preventing long term persistence of inflammation with associated complications.

Initial treatment for children with mild disease is local (topical steroid eye drops, peri- and intra-ocular steroid injections), followed by systemic treatment, if initial treatment fails to induce remission, with systemic steroids

Children in whom disease remission is not induced by treatment with topical, peri-ocular or systemic steroid, or who require prolonged treatment with high dose steroid in order to maintain remission, then proceed to treatment with a second line agent,

Historically, the use of systemic corticosteroids in uveitis was often in high doses for long periods of time (Howe et al 1994). This was associated with severe side effects in children, including dermatological (fragile skin, hirsutism, facial erythema, Impaired wound healing, striae etc); haematological (increase in total white blood count and promotes coagulation); endocrine and metabolic (growth suppression, fluid retention, inhibition of the immune system, changes in the electrolyte balance, weight gain, diabetes ); musculoskeletal (osteoporosis), gastrointestinal (peptic ulcer disease, candidiasis, and pancreatitis) (Stanbury et al 1998). Furthermore, topical ophthalmic, oral, and intravenous corticosteroids have also been associated with ocular side effects such as increased intraocular pressure, development of cataract,

glaucoma, and even retinal and choroidal emboli (Carnahan & Goldstein 2000, Thorne et al 2010). Therefore, the minimum dose necessary to control the disease should be given and prolonged use avoided.

The standard initial second line agent, for both JIA and uveitis, is Methotrexate (MTX).

There exists a significant group of children in whom uveitis cannot be controlled by tolerated levels of systemic steroid and methotrexate. Prior to the availability of Adalimumab and Infliximab such children were treated with other second line immunosuppressive agents, which were associated with more significant side effects and were not as effective in controlling uveitis. The existence of a cohort of children in whom IFRs are being requested for Adalimumab and Infliximab is testimony to the effectiveness of these agents.

The agents currently available for use in children whose disease is not controlled by tolerated doses of systemic steroid and methotrexate include Ciclosporin, Mycophenolate, Azathioprine, Tacrolimus and Cyclophosphamide, which are all themselves associated with severe side effects in children and were not underpinned by evidence from RCTs.

### **Anti-TNF Agents**

These new, agents are antibodies directed against Tumour Necrosis Factor  $\alpha$ , which is a cytokine which has been shown experimentally to be involved in the pathogenesis of uveitis. The currently available agents are Etanercept, Adalimumab, Infliximab, Golimumab and Certolizumab.

Of these treatments the following licensing and NICE approval exists:

- Etanercept is Licensed and approved by NICE for use in children with JIA;
- Adalimumab is licensed for use in JIA but is not currently NICE-approved
- Infliximab and Adalimumab are licensed and NICE-approved in adults with inflammatory arthritis
- Certolizumab and Golimumab are licensed but not currently NICE-approved in Adults with inflammatory arthritis.

Trial data suggests that Etanercept has no impact on disease activity in JIA uveitis. The onset of uveitis in a child on Etanercept for the treatment of JIA is therefore an indication to switch to an alternative agent. This agent is therefore not suitable for the treatment of JIA-Uveitis (JIA-U) and similar uveitis not associated with JIA

Adalimumab and Infliximab have been shown in RCTs to be highly effective in the treatment of JIA (see policy for use of anti-TNFs in JIA), with relatively few reported side effects. They are usually given in conjunction with methotrexate to

optimise their effect.

In addition to their effect in JIA, Adalimumab and Infliximab are felt by the international ophthalmology community to be highly effective in the treatment of JIA-U, and clinically similar childhood uveitis not associated with JIA (see supporting correspondence) Their use is supported by expert opinion, many reviews (Levy-Clarke et al 2013, Cordero-Coma et al 2013) published data and the Scottish Uveitis Network.

The use of Adalimumab and Infliximab has already become the standard-of-care in specialised uveitis services across the world.

The effect of Adalimumab and Infliximab on JIA-U has not been reported by the RCTs of their use in JIA, as children with JIA-U were excluded from taking part in these studies. The Sycamore trial (see below) is specifically addressing the use of adalimumab in JIA-U.

### **The SYCAMORE Trial**

The Sycamore trial (ISRCTN 10065623) is a randomised controlled trial (RCT) of the clinical effectiveness, safety and cost effectiveness of Adalimumab in combination with Methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis. The trial is funded by the NIHR Health Technology Assessment Programme and Arthritis Research UK. To date, 59/114 patients between 2 and 18 years have been randomised, and recruitment has been extended to December 2016. All participants will be treated for 18 months, with follow up of 3 years from randomisation. All participants will receive a stable dose of methotrexate and, in addition, either adalimumab or placebo by subcutaneous injection every 2 weeks.

## **2. Definitions**

**Uveitis:** Uveitis is the term used to describe inflammation of any structure within the eye. This policy is for the minority of cases with chronic sight threatening and visually disabling uveitis, refractory to topical and oral steroids and methotrexate.

**Infliximab:** Also known as Remicade is an anti-TNF alpha treatment licensed and NICE approved for the treatment of adults with inflammatory arthritis.

**Adalimumab:** Also known as Humira is an anti-TNF alpha treatment licensed and NICE approved for the treatment of adults with inflammatory arthritis. Adalimumab is also licensed (but not NICE approved) for the treatment of juvenile arthritis (JIA).

## **3. Aim and objectives**

This policy aims to:

- Specify the clinical circumstances whereby NHS England will commission Infliximab and Adalimumab to treat uveitis in paediatric



patients.

The objectives are to:

Clarify how the evidence and its quality determines the clinical commissioning position of NHS England for Infliximab and Adalimumab to treat uveitis in paediatric patients.

#### 4. Epidemiology and needs assessment

Children with Uveitis represent between 2% and 6% of the total uveitis population. The incidence of childhood uveitis in the general population of North America and Europe is estimated at 4.3-6/100,000, children, and the prevalence at 30/100,000; with the lowest incidence in the youngest children (Heiligenhaus et al 2013).

Association of Childhood Uveitis with Juvenile Idiopathic Arthritis

Uveitis in childhood can develop in association with various inflammatory arthropathies and in particular Juvenile Idiopathic Arthritis (JIA). Before the advent of uveitis screening for patients with JIA, and modern forms of treatment, rates of blindness in childhood uveitis were up to 30%. Despite recent changes in management and widespread screening, the risk of irreparable visual impairment remains high for such children.

20-25% of all uveitis in children is associated with Juvenile Idiopathic Arthritis (JIA). 12-38% of patients with JIA will develop uveitis within 7 years following the onset of uveitis.

Asymptomatic chronic anterior uveitis (CAU) associated with JIA has long been recognised as an important cause of visual loss in childhood with high levels of complications compared to other forms of anterior uveitis. The incidence of bilateral disease is between 67-85%. 0.5% of childhood blindness in England and Wales is caused by uveitis (Rahi 2013) – approximately 100 new presentations per annum, with other children visually impaired from complications of uveitis such as cataract and glaucoma.

Uveitis associated with JIA does not usually manifest with symptoms of red, painful eyes, and unless screening examinations are performed, the presentation of ocular disease is usually delayed until impaired vision due to complications of chronic intraocular inflammation is obvious. At this stage, it is often not possible to restore normal vision despite treatment. Because of the association with asymptomatic uveitis, children with JIA undergo regular screening eye examinations (RCOphth and BSPAR Joint Guidelines for screening of children with JIA for Uveitis).

Uveitis in JIA occurs predominantly in patients with early onset of arthritis, with a mean age in the onset of arthritis in children with JIA-U of between 3 and 5 years (Heiligenhaus 2007, Kotaniemi 1999). Young children are most at risk of delayed presentation as they are unable to articulate low grade symptoms of photophobia and floaters, and will only be diagnosed either by screening or by delayed

presentation with reduced vision due to complications of uveitis.

Uveitis may be presenting feature of JIA in 3-7% of patients (Dana MR 1997, Kanski JJ 1977), and in 50% develops simultaneously or within 6 months of the onset of arthritis (Heiligenhaus 2007). In such small children, because the symptoms of arthritis are usually more obvious than the symptoms of uveitis, there may be advanced ocular disease at the time of presentation, which is usually because of with joint swelling or impaired mobility rather than impaired vision, such that in 30-50% of children with JIA associated uveitis structural complications are present at diagnosis and 50-75% of those with severe uveitis will develop visual impairment secondary to the ocular complications detailed above.

**Chronic Uveitis in Childhood not associated with JIA**

A group of children exists with ocular disease clinically indistinguishable from JIA-U, who may or may not later develop JIA. This group is less well described, but includes the 3-7% of children in whom uveitis is a presenting feature of JIA.

**Effects of Visual Impairment on Childhood Development**

Visual impairment in childhood is a major disability, impacting on motor and cognitive development, education and emotional development and social relationships. There is a significantly increased prevalence of autism in visually impaired children. The effects are felt by the whole family and the child's life chances and opportunities are severely restricted.

## 5. Evidence base

A literature review was undertaken to establish the evidence base on clinically effectiveness, safety and cost-effectiveness of anti TNF  $\alpha$  agents Infliximab and Adalimumab in paediatric patients with idiopathic uveitis and uveitis secondary to Juvenile Idiopathic Arthritis (JIA). It identified 7 studies (reporting clinical efficacy and/or safety)- 2 Infliximab Tugal-Tutkun et al. 2008, Sukumaran et al 2012) 4 Adalimumab (Tynjala et al 2008, Kotaniemi et al 2011, Simonini et al 2013 and Magli et al 2013) and 1 comparative study which included both biological agents (Simonini et al 2011). No studies on cost-effectiveness were found.

### **Infliximab**

The evidence supporting the use of infliximab to treat uveitis in children with JIA or idiopathic uveitis is limited (SIGN level 3; Grade D). It is based on two retrospective case series studies with small sample sizes.

### **Adalimumab**

The evidence supporting the use of Adalimumab in children with JIA or idiopathic uveitis is limited as it comes from 4 case series studies with small sample sizes (SIGN level 3; Grade D).

### **Infliximab Vs. Adalimumab**

Evidence on the superiority of one agent over another is limited as it comes from one small comparative study (Simonini et al 2011) (SIGN level 3; Grade D).

There is a strong scientific rationale for the use of anti-TNF alpha agents based on what is known about the biology of uveitis through experimental models and experimental medicine (Caspi RR 2011, Dick et al 2004). Anti-TNF alpha agents have already become the standard of care in a range of inflammatory diseases with comparable biological mechanism, including severe ankylosing spondylitis and Crohn's disease (NICE TA143 and TA187).

The use of Infliximab and Adalimumab to treat uveitis is also supported by leading experts from Germany, the US France, Spain, Australia and Japan

The UK is playing a leading role in the conduct of these studies: including the multinational industry-sponsored VISUAL randomised controlled trials of Adalimumab in uveitis. Results from these trials are not expected until 2015 at the earliest.

A recent metanalysis undertook a pooled analysis of observational studies it identified in a review. It reported the proportion of responding children was 87% (95% confidence interval [95% CI] 75-98%) for adalimumab and, 72% (95% CI 64-79%) for infliximab,. There was no difference in the proportion of responders between ADA and INF ( $\chi^2 = 3.06$ ,  $P = 0.08$ ) (Simonini et al. 2013).

Levy et al (2014) undertook a study to provide recommendations for the use of anti-tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) biologic agents in patients with ocular inflammatory disorders for which a systematic review of published studies was performed and recommendations were generated using the Grading of Recommendations Assessment, Development, and Evaluation group criteria. The study concluded that Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease. Infliximab and adalimumab can be considered as second-line immunomodulatory agents for the treatment of uveitis associated with juvenile arthritis. Infliximab and adalimumab can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior uveitis, panuveitis, severe uveitis associated with seronegative spondyloarthritis, and scleritis in patients requiring immunomodulation in patients who have failed or who are not candidates for antimetabolite or calcineurin inhibitor immunomodulation. Infliximab and adalimumab can be considered in these patients in preference to etanercept, which seems to be associated with lower rates of treatment success.

In addition, another recent systematic review suggests that despite the fact that no RCT is available and the number of cases is small, there is evidence that switching to a second anti-TNF $\alpha$  agent results in improvement of ocular activity for the 75% treated children.(Simonini, et al. 2014b).

It is estimated that broader costs of blindness to the economy and society are equivalent to each patient requiring ten hospital admissions a year (RNIB Scotland, 2010) with lifetime costs for visually impaired children of £ 0.4-1.5 million

Testimonies from parents with children with Uveitis who have received Anti-TNF alpha treatment either through Individual Funding Requests or local commissioning arrangements prior to the creation of NHS England have been received in support of this clinical commissioning policy. These show the impact of Uveitis, the prolonged use of immunosuppressants and long-term steroid use and the effectiveness of Adalimumab or Infliximab in their individual cases. .

## 6. Rationale behind the policy statement

There is strong scientific rationale for the use of anti-TNF alpha agents based on what is known about the biology of uveitis derived from experimental models and experimental medicine studies. Use of infliximab and Adalimumab to treat uveitis is also supported by leading experts across the world; who all now incorporate this as standard practice, particularly in refractory patients.

## 7. Criteria for commissioning

### **Adalimumab/Infliximab in childhood ocular inflammation**

**Access to Adalimumab and Infliximab would be provided through specialised Uveitis networks with access to nationally recognised centres in this field.** These centres would work through regional networks with the support of the Ophthalmology Clinical Reference Group to ensure this standard of care was delivered equitably in full consultation with NHS England.

The policy supports recruitment into the ongoing Sycamore trial (Ramanan et al 2014) and Adalimumab or Infliximab will be used to treat Uveitis in patients who fulfil the following criteria:(See flow diagram):

- Children with JIA-U who fulfil the entry criteria (see below) to the Sycamore study should be offered entry into the study.
- Adalimumab will be available to children with Chronic Anterior Uveitis (CAU) whose ocular disease is of sufficient severity to fulfil the eligibility criteria for the Sycamore study, but who do not meet other eligibility criteria, for example because they do not have JIA, or because their ocular disease is too severe or unstable.
- Children exiting the Sycamore study should have access to anti-TNF as determined by the treating clinical team. This would be for those on placebo who flare or those who complete the trial and flare (e.g. found to be on Adalimumab after unmasking) or those exiting the trial due to other reasons in spite of having a response (such as need for urgent surgery for cataract or glaucoma).

Eligible children in whom Adalimumab is contraindicated because of allergy, intolerance, lack of effect or adverse social circumstances will be offered treatment with Infliximab

### **Ocular Inclusion criteria for entry into Sycamore Study**

- Active anterior uveitis, defined as a sustained grade of cellular infiltrate in the anterior chamber of SUN criteria grade  $\geq 1+$  during the preceding 12

- weeks despite MTX and corticosteroid (both systemic and topical) therapy
- They must have failed MTX therapy previously (minimum dose of 10-20mg/m<sup>2</sup> with a maximum dose of 25mg/m<sup>2</sup>).
- They must have been on MTX for at least 12 weeks and on a stable dose for 4 weeks

**Exclusion criteria for Sycamore study because ocular disease is too severe**

- Requiring more than 6 topical steroid eye drops per day,
- Requiring prednisone or prednisone equivalent at a dose >0.2mg/kg/day,
- Intraocular surgery within the 3 months prior to screening
- Intraocular or peri-ocular steroids within 30 days prior to screening
- Intraocular pressures < 6mmHg or > 25mmHg
- Intraocular pressure control requiring more than one topical pressure lowering therapy or requiring acetazolamide

**(Ramanan 2014):**

**Response definition:** Response to therapy should be assessed after 3 months of therapy and re-assessed every 3 months whilst treatment continues. It should document the current status of ocular inflammation.

**Treatment failure definition:** Is defined as in the protocol for the Sycamore trial (Ramanan 2014):

**Anterior segment inflammatory score grade (SUN criteria)**

- Two-step increase from baseline in SUN cell activity score (AC cells) over two consecutive readings
- Sustained nonimprovement with entry grade of 3 or greater for 2 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 (upon enrolment) ocular comorbidities (defined below) after 3 months
- Sustained scores recorded at entry grade measured over two consecutive readings (grade 1 or 2) still present after 6 months of therapy.

**Ocular comorbidities are defined as follows:**

- Optic disc swelling and/or cystoid macular oedema as gauged clinically and, where possible, by optical coherence tomography (OCT);
- Raised intraocular pressure (>25 mmHg) sustained over two consecutive visits without any response to a single ocular hypotensive agent;
- Ocular hypotony (low intraocular pressure <6 mmHg) sustained over two consecutive visits;
- Development of unexplained reduction in vision of 15 LogMAR letters over two consecutive visits.

### **Switching between Adalimumab and Infliximab**

Patients who do not achieve, or who fail to maintain, good control of their uveitis with Adalimumab will need to switch to Infliximab. This decision will be made by the consultant ophthalmologist and paediatric rheumatologist following full discussion with the child, carers, and the members of the specialist MDT.

## **8. Patient pathway**

Children with mild to moderate uveitis who have no sight threatening features (poor vision (<6/18); high inflammatory activity; uveitis onset before diagnosis of arthritis; <6 month interval between onset of arthritis and onset of uveitis; early onset of disease; long duration of uveitis; macular oedema; dense vitreous opacity; ocular hypotony (low intraocular pressure), and glaucoma (Kotaniemi 2008, Kanski 1997, Kanski 1990, Cabral 1994).) will be treated with topical corticosteroids by their local teams.

Children who present with, or develop, sight threatening features will be treated with periocular corticosteroid injection, and commenced on systemic steroid treatment, if appropriate by their local teams (including a paediatrician), and referred to the local specialist centre. Following assessment, children will be commenced on treatment with methotrexate by the local specialist centre if deemed appropriate.

Following 3 months treatment with an appropriate dose of methotrexate (or sooner in the event of methotrexate intolerance), children with persistent sight threatening features will be considered for treatment with Adalimumab by the specialist centre. Where appropriate children will be referred into the SYCAMORE trial at this stage.(see appendix 1).

In exceptional cases children with very severe features at presentation (hypotony, macular oedema, severe inflammation, cataract) will be considered for treatment with an Adalimumab immediately.

Children who are intolerant of or allergic to Adalimumab, will be considered for treatment with Infliximab. Children who respond to treatment with Adalimumab (as defined by reduction of inflammation to 0.5+ cellular activity or less) will continue treatment for 2 years at which time a trial of treatment withdrawal will be undertaken. If relapse occurs, restarting an anti-TNF will be considered,

In children where there is no reduction in inflammation in response to adalimumab after 3 months, Adalimumab will be withdrawn and consideration will be given to treatment with Infliximab. If there is no reduction in inflammation in response to Infliximab, it will be withdrawn

## **9. Governance arrangements**

Initiation of treatment with Adalimumab or Infliximab should always involve a suitably trained and experienced Consultant Ophthalmologist, a Consultant

Paediatric Rheumatologist and a paediatric-trained Clinical Nurse Specialist (CNS).

Adalimumab or Infliximab should not be used unless a patient has failed optimised treatment with Methotrexate (defined as 10-20mg/m<sup>2</sup> given subcutaneously once-weekly for at least 3 months).

When the patient is methotrexate intolerant an adequate trial (3 – 6 months) of an alternative conventional immunosuppressant should be given.

The optimum therapy will be individually chosen by the Consultant Ophthalmologist and Paediatric Rheumatologist following full discussion with the child, carers, and the specialist multidisciplinary team (MDT).

All children who commence treatment with Adalimumab or Infliximab should be offered the option of enrolling in the appropriate long-term registries. These registries are designed to provide long-term safety and outcome data for all these drugs

Specialised centres working through regional networks would continue to deliver anti-TNF alpha drugs through already established algorithms. These utilise specialist nursing models which exist in other specialties, to achieve concordance in standard of practice

## **10. Mechanism for funding**

All treatments for Uveitis up to and including the use of immunosuppressants are funded by Clinical Commissioning Groups.

The Anti-TNF alpha treatments , Adalimumab and Infliximab will be commissioned and funded by NHS England through designated specialist regional centres. New funding will be required to commission the Anti-TNF alpha treatments.

## **11. Audit requirements**

Specialised centres working through regional networks, will provide services with good clinical governance. Regular audit of practice will be carried out to drive up standards of care and evidence based practice established through ongoing clinical trials and to record patient outcomes.

## **12. Documents which have informed this policy**

Evidence review undertaken by NHS England.

Supporting letters from leading international uveitis experts.

Testimonies from parents of patients who have been prescribed Anti-TNF alpha treatment either via Individual Funding Requests or previous agreements prior to the formation of NHS England.

### **13. Links to other policies**

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

### **14. Date of review**

This policy will be reviewed in April 2016 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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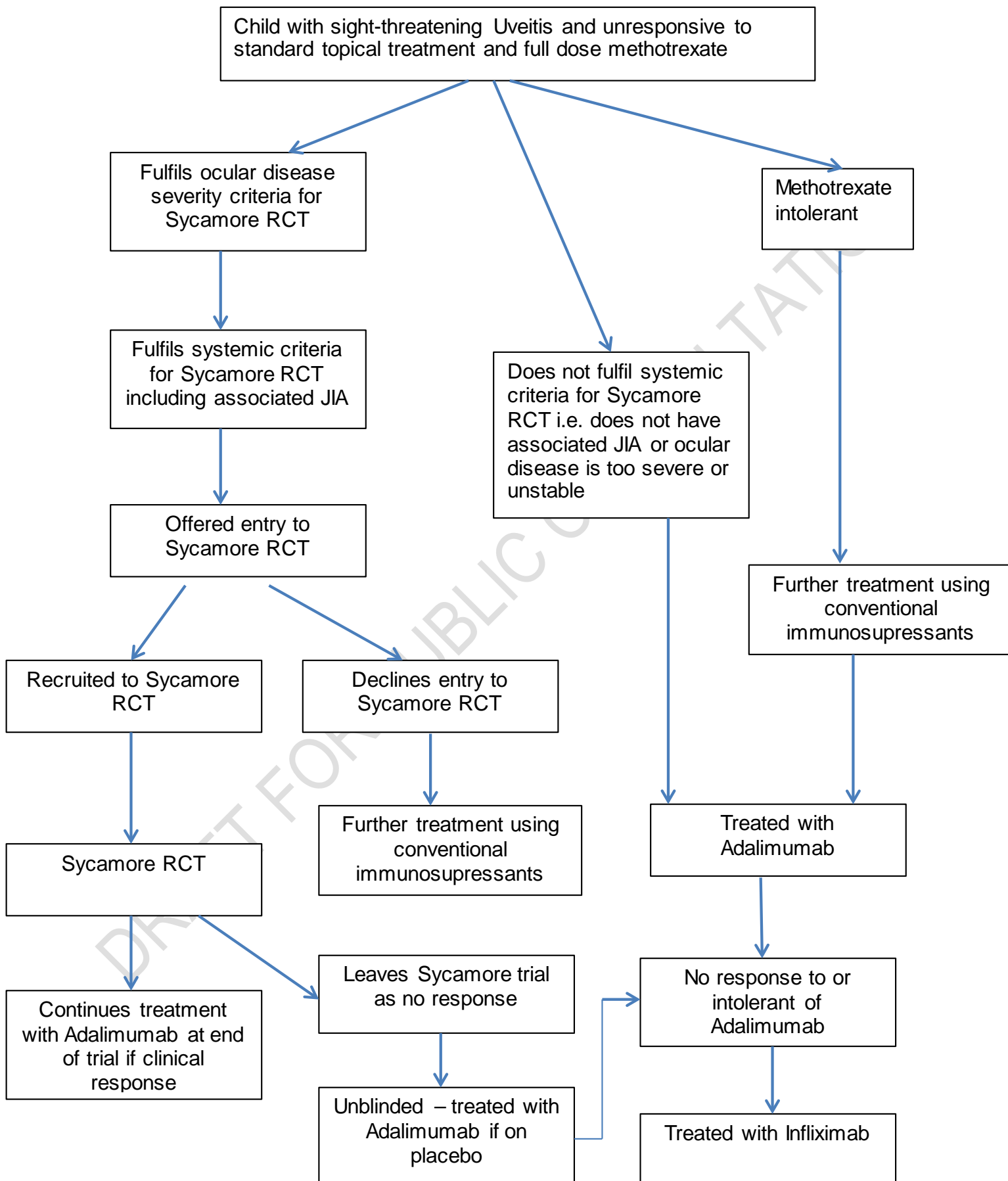
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## Appendix 1 Care Pathway



## **APPENDIX TWO – PATIENT TESTIMONIES (Paediatric)**

This section was added following comments by CPAG 1<sup>st</sup> October 2014.

### **Introduction**

The following are the words of children and their parents provided by Olivia's Vision, a charity established to help reduce the fears and anxiety felt by patients with a diagnosis of Uveitis. The words are those of the parents and children.

**“Uveitis means living on a knife edge”** Clair, mother to 20 year old Imogen, diagnosed at age 14.

### **Remission on Anti TNF**

*'My daughter F, was diagnosed with juvenile arthritis at 2 and uveitis at 4. She is 6 in January and has only just entered the first period of medically induced remission - well that's what I am calling it, but it's only been a month so far. Still it's as good as it has been since June 2010 and she's off drops so we are happy with that.'* (F continues to do well on Adalimumab).

*'C has just had his third infliximab infusion and - so far - it's been great. Apart from the pre-infusion shot of cortisone which gives him an itchy bottom (!), the actual infusion is painless, just time-consuming. For us it has been the best decision as he HATES his methotrexate injections to the point of aversion. His eyes are also clear for the first time ever!'*

### **Side effects of immunosuppressants.**

*'E is on her 6th week of MTX and has also been put on the immune depressant drug Ciclosporin. She is coping pretty well, good days and bad days. Usually the 3 days after taking her chemo, she finds it hard to even lift her head off the pillow, is on and off the toilet, and is very down, with some tearful moments. I find it hard to communicate with her on some of these days - she goes very inward, not talking, depressed, and extremely moody.'*

### **Steroid eye drops and complications.**

*'She was diagnosed with uveitis at 23 months and was treated with Pred forte drops for one year until she developed glaucoma from the chronic use of cortisone drops. Ever since she's been treated with MTX and off and on Pred forte. She has also been on glaucoma drops for the last 2 years. My beautiful daughter is now 6 and we discovered last Wednesday that the inflammation in her right eye was at 2+ and the pressure in her left eye was at 36. Further tests confirmed permanent irreversible damage to the optic nerve in the left eye with peripheral vision loss (tunnel vision). I don't know/understand how we got to this point seeing as she has had follow up visits every week to two weeks for the last 6 months but what's done is done. The doctor said surgery to alleviate the pressure is inevitable to prevent further damage and that in order to do the surgery the pressure has to come down. She is now on Maxidex, Pred forte, Xalatan, Combigan, Mydrilacil, MTX and Diamox and her rheumatologist wants to start her on Humira.'*

*'H was diagnosed with idiopathic bilateral uveitis when he was 3 and he is now almost 6. He developed steroid induced cataracts in both eyes but the one in his left is now so bad and his sight deteriorating that they are wanting to operate very soon. He seems to be very steroid responsive to the Maxidex that he has been mainly on for over 2 years and is probably responsible for the cataract and pressure issues.'*

### **Glaucoma Surgery**

*Following long absences from school after glaucoma surgery, 16 year old J was removed by the school from her 'A' Level courses. J is yet to complete her education due to further surgical complications.*

### **The need for ophthalmologic screening and the JIA child.**

*'My 7yr old daughter suffered JIA in her left knee some 4yrs ago. She was treated with steroid injections and the symptoms were relieved. She had 1 eye check during her initial treatment but I was not made aware of the requirement for 3 monthly screening and indeed the rheumatology team noted to our GP that future problems with her eyes were unlikely. I have now been informed by our current ophthalmic surgeon that the uveitis has most probably been present for approximately 2 years. My daughter's visual acuity was measured at 3/60 in her right eye and 4/60 in her left eye.'*

### **Anxiety, the need for counselling and for emotional support.**

The children:

*'I am J. I have been ill for a year and get very sick and tired. I have a lot of pain and cry a lot. I have a special computer in school to write on with big letters and have books with big letters on. I hate being ill and have lots of days off school. Mum said I'm brave.'*

*'A few months ago my friends made fun of my health, and told me things like I had stupid coloured eyes (one of my eyes is blue and the other brown), that they didn't care what ever was going on with my health, and continued to cyber bully me until I eventually did something about it and it was dealt with.'*

Their parents:

*'It has hit me, in particular, recently how long we have been on this rollercoaster with N and wondering if or when it will ever end. It feels like every day is a treadmill. Will she ever be able to lead a normal life? Will she be able to have children when she is older? Will she actually be able come off medication for long enough to allow that to happen? Will she go blind?' (Mother of a sixteen year old).*

*'Needless to say... I am going to try some anti- depressants for a bit. Would like to manage a bit of an even quell.' (Mother of a six year old whose uveitis is caused by chicken pox).*

*'I haven't been on the forum for many months. I apologize to all my forum friends for my silence. I tend to be silent when the hurt is at its worst. B had to be admitted to a psychiatric hospital for repeated attempts to harm himself and talks of suicide. He says he'd rather die than have JIA anymore. Can we have a discussion on how*

*uveitis affects mental health and ways to cope?* (B, aged 8, did not adjust to blindness).

### **Case study**

The following case history was included in the stakeholder submission from the Royal National Institute for Blind People (RNIB)

C, aged ten.

**Background:** C was aged two when he was diagnosed with hypermobility which it is thought to have some connection with the development of the uveitis he has since suffered.

C's uveitis was uncontrolled for a number of years and he was put onto high dose steroids. C's behaviour was affected by the steroid and he became very aggressive – he also suffered weight gain. The steroids caused C to develop cataracts which meant he has now had to have lensectomies and consequently wears very high prescription glasses which restrict the activities that he can take part in – such as sports.

C's uveitis remained uncontrolled for some time and due to the sight loss he has suffered C is unable to play outside, particularly as it is dangerous for him to cross roads unsupervised.

C had to have 20 operations and at the height of his problems with uveitis he had to visit the eye hospital every two weeks which meant that he was frequently missing school. Due to his age he also required a carer to attend the hospital visits making it difficult for his mother to maintain paid employment.

**Effect of new treatment:** Two years ago, C was put onto anti-TNF treatment which has successfully controlled his uveitis.

C's vision has now been stabilised. C is able to attend a main stream school where he is able to read larger print and read the whiteboards at school with his remaining vision. C enjoys watching TV and playing with his X-box.

He now needs to attend the eye hospital only every two months and a district nurse visits him every two weeks to administer the injections. C does not mind having the injections and the visit from the District Nurse is convenient for him and his family.

The effects of the steroids have worn off and C is no longer aggressive and his weight is maintained. C does not suffer any adverse effects from the anti-TNF treatment.

If C could not access the ant-TNF treatment his vision would be likely to deteriorate and his quality of life and ability to find work severely weakened. He would also be at risk of further complications, such as glaucoma.

### **Appendix 3.**

#### **Cost Effectiveness of Anti-TNF alpha treatment in ocular inflammatory disease including Uveitis**

Further information on cost effectiveness of anti-TNF alpha treatments as requested by CPAG (1<sup>st</sup> October 2014)

#### **Purpose of this submission.**

1. To provide a model for evaluation of cost effectiveness of Anti-TNF alpha treatment in ocular inflammatory disease, including Uveitis.
2. To estimate the total NHS cost of providing this service

#### **International guidelines**

Guidelines for the use of anti TNF agents have been produced by Scotland, Germany and the US using a similar literature base to this submission.(Heiligenhaus, Michels et al. 2012, Levy-Clarke, Jabs et al. 2014). There is a universal consensus on the need to use anti TNF agents in refractory cases of uveitis and that the strongest evidence base exists for infliximab and adalimumab.

#### **Children**

A recent meta-analysis confirms a treatment effect of 85% for infliximab and adalimumab in childhood chronic uveitis (Simonini, Katie et al. 2013, Semeraro, Arcidiacono et al. 2014).

A 75% response rate using infliximab or adalimumab following previous poor response to an anti-TNF agent suggests treatment switching between biologics is no less effective than in arthritis,(Simonini, Katie et al. 2014).

As switching between anti TNF agents has no cost implications, these two papers imply that 96% of patients started on one agent, and then if necessary, switched to a second agent, will respond.

#### **Cost of disease**

#### **Blinding conditions costed by NICE**

The visual outcome of uveitis is similar to that covered in NICE guidance on treatments of AMD, diabetic retinopathy and retinal vein occlusion with the following provisos.

Some forms of uveitis result in complete blindness and enucleation of the affected eye with additional costs of discomfort and disfigurement.

Some forms of uveitis have a risk of requiring surgery which requires additional costing. The results of surgery in these conditions usually have considerable added

risk to the routine outcomes of these surgeries. The costs of surgery as a complication of treatment [but not the underlying condition] are dealt with in the Ozurdex NICE TA

### **Problems with asymmetrical ocular risk of blindness**

There continues to be debate about the relative costs of monocular versus binocular visual loss. It is thought that the health costs of monocular visual loss are only significant when the vision in the worst eye falls to 6/60 or less. This makes costing of disease that remains unilateral different to conditions such as AMD where bilateral involvement is usually inevitable.

The additional risk of bilateral visual loss, from any condition that results in monocular loss, is increased over a lifetime from 1% to 5%. Those with childhood onset monocular visual loss, from whatever cause, are at considerably greater lifetime risk of bilateral visual loss than the elderly. One approach to costing unilateral visual loss is to calculate it as a 4% cost of lifetime bilateral blindness.

The majority of the costs of blinding disease are in those with binocular blindness as this most closely relates to quality of life and social costs. It is however inconceivable ethically to leave monocular disease untreated and it is accepted practice to average the costs of blindness over those who suffer from unilateral disease with those who suffer bilateral disease.

### **Problems costing children**

Children are at risk of amblyopia, special educational needs and any visual loss has a lifelong cost considerably higher than those affected by conditions presently costed by NICE –which are generally conditions of middle age or the elderly. Surgical intervention in children with uveitis have a much higher complication rate than similar surgery in adults with uveitis.

If costs are age-weighted towards usual years of employment then those with visual loss before twenty need to be weighted higher than those blinding conditions such as AMD presently costed by NICE.

The costs of blindness in the elderly are mostly based on the costs of residential care, whereas the costs of blindness in children need to include special education, reduced lifetime earnings as well as possible residential care. There is also the potential impact on the earnings of parents.

### **Assumed costs of treatment**

Drops and monitoring £725 per year

MTX and drops and monitoring £1700 per year

MTX and drops and biologic and monitoring £11000 per year



Surgery £2000 per event

**Time horizon for treatment:** it is likely that the minimum time for effective treatment with systemic immunosuppression in paediatric Chronic Anterior Uveitis is 3 years – one year to obtain remission and continuation for two years of remission to reduce chances of relapse following discontinuation of treatment. [ref de Boer on MTX use in JIAU]. Average length of treatment is assumed to be [3-] -5- [10] years.

### **Population size**

**The total population under treatment is determined by the incidence of the relevant population and the length of prescribing the treatment.**

It is possible that earlier aggressive treatment will reduce the length of treatment required. The optimal time for treatment effectiveness is not known and may be very different from the time of optimal cost-effectiveness as it is difficult to distinguish completely, at baseline, those who will undergo late remission without complications.

Most reported case series have used anti-TNF alpha treatment as a rescue treatment in patients who have continuing activity on steroids with one or two conventional immunosuppressants i.e. there is likely to have been a prolonged period of poor disease control prior to study entry and this is highly likely to reduce the efficacy of any change in treatment.

### **Estimates of relevant population size**

The total populations under consideration [those with uveitis] are stable with no evidence of an increasing incidence worldwide, despite the rising incidence of other autoimmune diseases.

The indications for systemic immunosuppression, and the relative contraindication of chronic oral and topical steroid use have been changing for the last thirty years and there are significant differences noted in the use of systemic steroids in the adult uveitis population in the USA compared to Europe.

There is little evidence of an increasing use of systemic immunosuppression for UK patients over the last ten years. There are established referral patterns for patients requiring these drugs and the inappropriate use of prolonged oral and topical steroids by non-specialists is now a comparative rarity.

Estimates of the incidence of failed response to the initial conventional immunosuppressant from tertiary referral centres is likely to be robust. There is unlikely to be a hidden population of patients with unreferral patients with poorly controlled disease.

As referral is usually made at the time the initial immunosuppressant is required, then there is likely to be little variation in the indications for treatment change as a result of primary treatment failure. There have been no significant differences in the

efficacy of all the conventional immunosuppressants used in uveitis over the last 15 years and so the proportion of patients classed as treatment failures is likely to be an accurate estimate of the lifetime need for treatment

The increased use of early MTX has occurred since 1996. In most International centres of uveitis anti TNF agents have been available for ten years. There is no evidence of a significant difference in the proportion of childhood uveitis that has been treated with biologics [10-20%].

This is based on clinical experience in the UK, Holland, Germany. US and Finland.

If you assume that 75% of patients are given MTX and MTX has a 73% effect – then you would predict 20% of the whole population would be MTX failures.

### **Health Cost of blindness**

#### **QALY for visual loss**

Baseline	0.97
Mild visual loss, or severe unilateral visual loss	0.76
Moderate visual loss	0.63
Severe visual loss	0.53.

The PDT study found a five letter drop led to 0.0058 drop in QoL and this means a drop from normal vision to <1.3 leads to a drop of 0.406 in QoL (Reeves, Langham et al. 2009).

We have taken the loss of QoL to be 0.44 if the patient's vision drops from normal to <6/60.

#### **Time horizon**

The life expectancy after blindness from paediatric uveitis is taken to be 75 years so the difference in QALYs resulting from childhood blindness is  $75 \times 0.44 = 33$

The life expectancy at 16 would be 67 years and for adults with uveitis an estimated 35 years

### **Financial Costs of blindness**

Financial costs of blindness include NHS costs and non-NHS costs; the latter are recommended to be costed separately. The range in the literature of direct costs is £1-8,000 pa

Indirect costs are estimated at £14,700 for each registration at 2013 prices .[RNIB data 2013]

The cost of blindness per year used in the Lucentis costings for AMD is £6,500, but there is poor uptake of health resources in this population. There are also considerable differences in the nature of non-NHS costs. There will be no element of cost for loss of employment in this age group, and there is a considerable difference in life expectancy.

The ongoing social costs of mild visual impairment may amount to loss of potential earnings only whereas for those with severe visual impairment they include loss of employment and the need for continuous care then the financial cost will rise to £40,000 pa.

The range of costs is therefore £1,000 to £40,000

The lifetime cost of childhood blindness is taken to be  $75 \times £6,500 = £487,500$ .

Adults are assumed to have a life expectancy of 35 years after visual loss. The cost of adult blindness in this group is therefore  $35 \times £6500 = £227,500$ .

### **Published rates of blindness in JIAU**

There are considerable differences in the rate of blindness in the contemporary literature ranging from none [Finland] to 25% [USA] over three years. Most of this variation can be explained by the length of follow up and the level of morbidity in the cohort at referral. The Great Ormond Street cohort finds the peak rate of blindness to be ten years after onset and that there is a continuing risk of cataract surgery for 25 years, so short term studies of unrepresentative cohorts need careful assessment when used as evidence of variations in lifetime visual morbidity.

For the purposes of this analysis the frequency of **lifelong** blindness caused by uveitis is required.

(Edelsten, Lee et al. 2002, Thorne, Woreta et al. 2007, Woreta, Thorne et al. 2007, Holland, Denove et al. 2009, Kalinina Ayuso, Ten Cate et al. 2010, Gregory, Kempen et al. 2013, Kotaniemi, Sihto-Kauppi et al. 2014)

Some variation in reported rates of blindness will be due to the different availability and prescribing of immunosuppressive treatments. This can give some indication of the effectiveness of contemporary management, if not treatment types through using historical controls.

We have also used unpublished data of 310 Great Ormond Street patients with onset of disease from 1986 to 2008

### **Bilateral blindness rates estimated at ten years from the literature**

Site	Result format	10yr frequency
Finland	6 years follow up, 1% freq	1.8%
GOS	10 year rate low risk	1.2%

Ayuso, 5 year follow up	4% freq at 5 years	8%
GOS 10 year high risk	35% pe, 4.6% rate pa	9.1%
Woreta, 6 year from onset	14% freq at 6 years, rate 9% pa	30%
Holland, 2 year from onset	7% rate at 2yr, 20% rate at 5 yr pp	32%

### **Risk factors for blindness and relationship to treatment changes in disease activity.**

Sight is lost from damage prior to treatment and from persistent activity due to poor treatment response. The main complications are initially cataract surgery and then subsequent hypotony, maculopathy retinal detachment or glaucoma. The risks of blindness are virtually confined to those who have undergone cataract surgery at some point. Lifelong risks of blindness can then be predicted from the risks of cataract surgery. Cataract surgery is virtually unknown in those who undergo early remission. Lifelong risks of cataract can then be predicted from the level of damage at presentation and the length of active disease.

Most descriptions of treatment effects consist of 6-12 month reports of levels of disease activity and are unlikely to be able to report significant changes in the rates of long term complications such as surgery and visual loss. The rates of these complications are more likely to be influenced by events prior to the study recruitment. The majority of reports have a wide range of prior treatments which makes interpretation of subsequent treatment effects complex and difficult to extrapolate to different regions.

The GOS cohort describes patients from the onset of disease and contains patients treated from onset as well as referrals. In the period studied there has been an increasing rate of early use of MTX and infrequent use of alternative agents for uveitis as initial treatment.

It is assumed for this study that the initial treatment of those not manageable by topical treatment will be a single conventional immunosuppressants and/or systemic steroids. In children this will be MTX in the majority of cases.

<b>Health state</b>	<b>Good prognosis</b>	<b>Poor prognosis</b>
Remission	45%	20%
Active	26%	13%
Cataract	26%	36%
Cataract+blind	3%	31%

If the population consists of 40% with poor prognosis then overall frequency of blindness is 14%. In most studies 40% of JIAU patients present with posterior synechiae.

A population of those failing on MTX at 12 months would consist of 90% poor prognosis with an estimated frequency of blindness of 28% overall.

### **Lifelong risk of blindness**

There is a continuing risk of cataract surgery from 15 years to 25 years. A competing risk model for cataract surgery [with remission as the competing risk] estimates 52% will undergo cataract surgery by 25 years from onset of disease. The risk of blindness following late cataract surgery is likely to be less than following cataract surgery at a young age.

### **The problem of unilateral disease**

In a minority of patients, uveitis will remain unilateral. The main health cost is secondary to bilateral visual loss. It is not possible to only treat [and model] those with bilateral disease, not only because it is unethical, but also because unilateral blindness increases the risk of bilateral blindness from other conditions occurring in the other eye. Therefore the whole population of those at risk is included in the analysis accounting for the lesser, but measurable risk of lifelong blindness in those with unilateral disease.

The literature is inconsistent in reporting complications per eye per patient and in unilateral vs bilateral disease when performing cost effectiveness studies.

As it is inconceivable to NOT treat unilateral disease, it is appropriate to include those with unilateral disease with an appropriate reduction in their health costs.

It is likely that the lifetime risks of blindness per eye are 4% for good prognosis and 35% for poor prognosis groups, and the lifetime risk of bilateral blindness is 0.3% in good prognosis groups and 12% in poor prognosis groups

### **Treatment effects of anti TNF agents in defined populations of uveitis patients failing on a conventional immunosuppressant.**

#### **Effect of anti TNF**

The best estimate of treatment effect is 85% at one year for disease control. It is assumed that a further 10% can enter remission with switching biologics. It is assumed that there will be a relapse rate of 5% per year.

The range of the effect is taken to be 60-95%

The probability of blindness following anti TNF treatment is taken to be 1%

### **Effect of continuing conventional treatment**

It is assumed that the alternative treatment is continuing MTX [in children] or other immunosuppressant with concomitant steroid use, and that the treatment has been tried for a year before establishing that the patient is a treatment failure, defined as no remission >3m. The treatment effect of MTX is 0.73[0.67-0.81] with a median time to remission of 3m

The estimated outcome after ten years is that 10 % [5-40] will go into remission and 90% [85-95] will remain active.

The probability of blindness continuing conventional treatment is taken to be 15%

### **Effect of swapping conventional immunosuppressants.**

It is assumed that swapping to, or adding a conventional immunosuppressant will result in disease control in 50% of this population with a subsequent probability of blindness of 8%.

### **The economic justification for biologics**

In order to provide equity the cost effectiveness of treatments should be in line with treatments for blinding conditions within the NHS, and the levels of risk acceptable in line with the uncertainty expected in other disease states. For example, the debate about statins is presently centred on whether a 10 or 20% risk of heart disease over ten years is an acceptable level to start treatment.

An assumption has been made that a 1% risk of blindness is an upper limit of acceptance – which equates to an 8% risk of unilateral blindness – which equates to a 32% risk of cataract in any eye.

### **Economic model –further assumptions**

Willingness to pay £35,000 [range £15-45,000]

Five treatment strategies are compared.

1 continue MTX risk blindness 15%

2 add a conventional immunosuppressant at cost £15,000 for five years, risk blindness 8%

3 add a biologic at cost £45,000 over five years, risk blindness 1%

4 add a biologic at cost £90,000 over ten years, risk blindness 1%

5 add a biologic cost £45,000, risk blindness 8%

## Results

The two dominant strategies were strategies 2 and 3. The favoured strategy was 3 with a Probabilistic Incremental Cost-Effectiveness Ratio (ICER) over strategy 2 of £6,400. The results were similar when the willingness to pay was reduced to £15,000. The net monetary benefit of strategy 2 was then £238,700.

A Tornado plot found the greatest drivers were the total cost of biologic treatment and the risk of blindness on a biologic.

Sensitivity analysis suggested biologic treatment was preferred up to a total of 9 years treatment when the ICER versus conventional immunosuppression rose to £22,000 and up to a risk of blindness on this treatment of 4%. When the risk of blindness on biologic rose to 5% the ICER rose to £40,200.

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## References

Edelsten, C., et al. (2002). "An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood." Br J Ophthalmol **86**(1): 51-56.

**BACKGROUND/AIMS:** The clinical course for childhood chronic anterior uveitis can vary from mild, self limiting disease to bilateral blindness. The purpose of this study was to identify those risk factors at onset that predict disease severity. **METHODS:** A retrospective case note review of all patients with painless anterior uveitis diagnosed from 1982 to 1998. Patients were divided into two cohorts based on route of referral, diagnosis, and compliance with treatment. The standard cohort consisted of only those diagnosed from routine screening of juvenile idiopathic arthritis. **RESULTS:** Complications- cataract surgery, ocular hypertension treatment, and visual acuity <6/24. Remission: inactive uveitis on no topical treatment for >6 months. Results-163 patients were included. 34 patients (21%) developed at least one complication. The most significant predictor of complications was severe disease at onset ( $p = 0.001$ ). Other factors included uveitis at the first examination ( $p = 0.034$ ), membership of the non-standard cohort ( $p = 0.0001$ ), non-oligoarticular disease ( $p = 0.02$ ), and late onset arthritis ( $p = 0.024$ ). Male sex was associated with increased complications in the standard cohort ( $p = 0.001$ ). Factors predisposing to remission included membership of the standard cohort ( $p = 0.003$ ), onset after 1990 ( $p = 0.016$ ), white race ( $p = 0.015$ ), mild disease onset ( $p = 0.003$ ), and a long gap between arthritis and uveitis onset ( $p = 0.015$ ). **CONCLUSIONS:** It is possible to characterise the severity of those with childhood chronic anterior uveitis at the onset of disease. The majority of patients remit without visually disabling complications. It may be possible to reduce the complication rate by targeting aggressive immunosuppression on high risk patients before complications develop.

Gregory, A. C., 2nd, et al. (2013). "Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the Systemic Immunosuppressive Therapy for Eye Diseases Study." Ophthalmology **120**(1): 186-192.

**PURPOSE:** To describe the incidence of and risk factors for visual acuity (VA) loss and ocular complications in patients with juvenile idiopathic arthritis (JIA)-associated uveitis. **DESIGN:** Multicenter retrospective cohort study. **PARTICIPANTS:** A total of 327 patients (596 affected eyes) with JIA-associated uveitis managed at 5 tertiary uveitis clinics in the United States. **METHODS:** Participants were identified from the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) cohort study. Demographic and clinical characteristics were obtained for every eye of every patient at every visit via medical record review by trained expert reviewers. **MAIN OUTCOME MEASURES:** Loss of VA to 20/50 or to 20/200 or worse thresholds and the development of ocular complications. **RESULTS:** At presentation, 240 eyes (40.3%) had a VA of  $\leq 20/50$ , 144 eyes (24.2%) had a VA of  $\leq 20/200$ , and 359 eyes (60.2%) had at least 1 ocular complication.



The incidences of VA loss to the  $\leq 20/50$  and  $\leq 20/200$  thresholds were 0.18 and 0.09 per eye-year (EY), respectively; the incidence of developing at least 1 new ocular complication over follow-up was 0.15/EY (95% confidence interval [CI], 0.13-0.17). However, among eyes with uveitis that had no complications at presentation, the rate of developing at least 1 ocular complication during follow-up was lower (0.04/EY; 95% CI, 0.02-0.06). Posterior synechiae, active uveitis, and prior intraocular surgery were statistically significantly associated with VA to the  $\leq 20/50$  and  $\leq 20/200$  thresholds both at presentation and during follow-up. Increasing (time-updated) anterior chamber cell grade was associated with increased rates of visual loss in a dose-dependent fashion. Use of immunosuppressive drugs was associated with a reduced risk of visual loss, particularly for the  $\leq 20/50$  outcome (hazard ratio, 0.40; 95% CI, 0.21-0.75;  $P < 0.01$ ). CONCLUSIONS: Ocular complications and vision loss were common in our cohort. Increasing uveitis activity was associated with increased risk of vision loss, and use of immunosuppressive drugs was associated with reduced risk of vision loss, suggesting that control of inflammation and use of immunosuppression may be critical aspects in improving the outcomes of patients with JIA-related uveitis. FINANCIAL DISCLOSURE(S): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Heiligenhaus, A., et al. (2012). "Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis." Rheumatol Int **32**(5): 1121-1133.

Uveitis in juvenile idiopathic arthritis (JIA) is frequently associated with the development of complications and visual loss. Topical corticosteroids are the first-choice therapy, and immunosuppression is commonly used. However, treatment has not been standardized. Representatives from the German Ophthalmological Society, Society for Childhood and Adolescent Rheumatology, and the German Society for Rheumatology reached consensus on a standardized treatment strategy according to disease severity in the individual patient. The recommendations were based on a systematic literature analysis in MEDLINE and consensus expert meetings. Evidence and recommendations were graded, and an algorithm for anti-inflammatory treatment and final statements confirmed in a Delphi method. An interdisciplinary, evidence-based treatment guideline for JIA uveitis is presented.

Holland, G. N., et al. (2009). "Chronic anterior uveitis in children: clinical characteristics and complications." Am J Ophthalmol **147**(4): 667-678 e665.

PURPOSE: To describe clinical features of chronic anterior uveitis in children at presentation to a referral center (baseline); to identify relationships between demographic, medical, and ophthalmic factors at baseline; and to determine baseline factors that predict new complications and vision loss during follow-up. DESIGN: Retrospective case series. METHODS: Studied were involved eyes of all children (age  $<$  or  $= 16$  years at disease onset) with chronic anterior uveitis who were examined by 1 clinician from 1993 through 2006. Cross-

sectional analyses compared baseline findings. Relationships between potential risk factors and incident adverse events (new complications, vision loss) were studied by Kaplan-Meier and Cox proportional hazards regression models. RESULTS: There were 115 patients (200 eyes) who met inclusion criteria. Follow-up (n = 83 patients) ranged from 0.4 to 157.5 months (median, 23.5 months). There were numerous strong relationships between 8 defined complications at baseline in pairwise comparisons. Flare was the inflammatory sign most consistently associated with complications at baseline. Baseline factors that predicted new complications during follow-up included age  $\leq$  3 years, elevated cells, elevated flare, keratic precipitates, signs of intermediate uveitis, and papillitis (all  $P < .043$ ); factors that predicted vision loss included male gender, increased flare, signs of intermediate uveitis, papillitis, and baseline complications (all  $P < .015$ ). Not related to new complications were presence of juvenile idiopathic uveitis and immunomodulatory therapy. CONCLUSION: Chronic anterior uveitis in children is associated with various vision-threatening complications that occur in combinations. Complications develop early in the disease course. Patients with more severe disease at presentation are at increased risk of additional adverse events.

Kalinina Ayuso, V., et al. (2010). "Male gender and poor visual outcome in uveitis associated with juvenile idiopathic arthritis." Am J Ophthalmol **149**(6): 987-993.

PURPOSE: To analyze visual outcome in uveitis associated with juvenile idiopathic arthritis (JIA) according to age of onset of uveitis, gender, and initial manifestation of JIA. DESIGN: Retrospective nonrandomized interventional case series. METHODS: Visual outcome of 117 affected eyes (65 patients) with JIA-associated uveitis was noted at onset of uveitis and after 1, 3, and 5 years. Visual outcome was analyzed according to gender, age of onset of JIA-associated uveitis ( $<7$  years and  $>7$  years), and initial manifestation of JIA (as uveitis or as arthritis). Linear and logistic regression with generalized estimating equation (GEE) was performed. RESULTS: Median age of onset of uveitis was 4.2 years (range 1.5-16). Female-to-male ratio was 3:1. In 15 children (23%) uveitis was diagnosed before arthritis. Visual acuity of boys was significantly worse at 1 and 3 years of follow-up (both  $P \leq .03$ ) but not at 5 years of follow-up ( $P = .45$ ). Until 3 years after the diagnosis of uveitis, children with atypical initial manifestation of JIA (uveitis before arthritis) had significantly worse visual acuity compared with children in whom uveitis debuted after arthritis (all  $P \leq .05$ ). No difference in vision between younger-onset ( $<7$  years) and older-onset ( $>7$  years) groups was noted. Blindness was independently associated with male gender (odds ratio [OR] = 6.61; 95% CI: 1.02-42.98;  $P = .048$ ). CONCLUSIONS: Male gender was an independent risk factor for poor visual prognosis in JIA-associated uveitis. Children in whom uveitis is being diagnosed before arthritis have significantly worse vision until 3 years after uveitis onset.

Kotaniemi, K., et al. (2014). "The frequency and outcome of uveitis in patients with newly diagnosed juvenile idiopathic arthritis in two 4-year cohorts from 1990-1993 and 2000-2003." Clin Exp Rheumatol **32**(1): 143-147.

**OBJECTIVES:** To retrospectively compare the frequency and outcome of uveitis between two cohorts of patients with newly-onset juvenile idiopathic arthritis (JIA) separated by a 10 year interval. **METHODS:** The diagnosis of JIA was made in 239 patients in 1990-1993 and in 240 patients in 2000-2003 by paediatric rheumatologists at the Rheumatism Foundation Hospital, Heinola, Finland. An ophthalmologist examined all the patients regularly and diagnosed uveitis. The demographics of the patients, type of JIA, frequency, medical treatment and outcome of uveitis were documented. **RESULTS:** The main outcome measures were the frequency and outcome of uveitis, the number of complications and the best corrected visual acuity (BCVA), need of corticosteroids and other immunosuppressive treatment. The frequency of uveitis was higher (25% vs. 18%) in the earlier cohort. The visual outcome was  $\geq 0.5$  in all JIA-uveitis patients except one in the earlier cohort. Complications were fewer (21% vs. 35%) and uveitis was milder according to the Standardisation of Uveitis Nomenclature (SUN) criteria in the later cohort. Remission of uveitis (33% vs. 42%) and arthritis (20% vs. 23%) in JIA-uveitis patients was similar in both cohorts after a follow-up of 6.6 and 5.9 years, respectively. Systemic corticosteroids were more commonly used (25% vs. 7%) in JIA-uveitis patients of the earlier cohort but the use of methotrexate was equal in both cohorts (65% vs. 67%). **CONCLUSIONS:** In this study with early and aggressive treatment and close monitoring the outcome of JIA-uveitis patients was favourable and visual loss was avoided in most cases.

Levy-Clarke, G., et al. (2014). "Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders." Ophthalmology **121**(3): 785-796 e783.

**TOPIC:** To provide recommendations for the use of anti-tumor necrosis factor alpha (TNF-alpha) biologic agents in patients with ocular inflammatory disorders. **CLINICAL RELEVANCE:** Ocular inflammatory diseases remain a leading cause of vision loss worldwide. Anti-TNF-alpha agents are used widely in treatment of rheumatologic diseases. A committee of the American Uveitis Society performed a systematic review of literature to generate guidelines for use of these agents in ocular inflammatory conditions. **METHODS:** A systematic review of published studies was performed. Recommendations were generated using the Grading of Recommendations Assessment, Development, and Evaluation group criteria. **RESULTS:** Numerous studies including controlled clinical trials have demonstrated that anti-TNF-alpha biologic agents (in particular infliximab and adalimumab) are effective in the treatment of severe ocular inflammatory disease. Based on these studies, the expert panel makes the following recommendations. **CONCLUSIONS:** Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behcet's disease. Infliximab and adalimumab can be considered as second-line immunomodulatory agents for the treatment of uveitis associated with juvenile arthritis. Infliximab and adalimumab can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior uveitis, panuveitis, severe uveitis associated with seronegative spondyloarthritis, and scleritis in patients requiring immunomodulation in patients who have failed or who are not

candidates for antimetabolite or calcineurin inhibitor immunomodulation. Infliximab and adalimumab can be considered in these patients in preference to etanercept, which seems to be associated with lower rates of treatment success.

Reeves, B. C., et al. (2009). "Verteporfin photodynamic therapy cohort study: report 2: clinical measures of vision and health-related quality of life." Ophthalmology **116**(12): 2463-2470.

**PURPOSE:** To quantify decreases in health-related quality of life (HRQoL) for given deterioration in clinical measures of vision; to describe the shape of these relationships; and to test whether the gradients of these relationships change with duration of visual loss. **DESIGN:** A prospective, longitudinal study of patients treated with verteporfin photodynamic therapy in the United Kingdom National Health Service. **PARTICIPANTS:** Patients with neovascular age-related macular degeneration (AMD) treated in 18 ophthalmology departments in the United Kingdom with expertise in management of neovascular AMD. **METHODS:** Responses to HRQoL questionnaires (Short Form 36 [SF-36] and National Eye Institute Visual Functioning Questionnaire [NEIVFQ]) and clinical measures of vision were recorded at baseline and at follow-up visits. Mixed regression models were used to characterize the relationships of interest. **MAIN OUTCOME MEASURES:** Measures of vision were best-corrected visual acuity (BCVA) and contrast sensitivity (CS). The SF-36 physical and mental component scores (PCS and MCS), SF-6D utility, and distance, near, and composite NEIVFQ scores were derived to characterize HRQoL. **RESULTS:** The SF-6D, PCS, and MCS were linearly associated with BCVA; predicted decreases for a 5-letter drop in BCVA in the better-seeing eye were 0.0058, 0.245, and 0.546, respectively (all  $P < 0.0001$ ). Gradients were not influenced by duration of follow-up. Models predicting distance, near, and composite NEIVFQ scores from BCVA were quadratic; predicted decreases for a 5-letter drop in BCVA in the better-seeing eye were 5.08, 5.48, and 3.90, respectively (all  $P < 0.0001$ ). The BCVA predicted HRQoL scores more strongly than CS. **CONCLUSIONS:** Clinically significant deterioration in clinical measures of vision is associated with small decreases in generic and vision-specific HRQoL. Our findings are important for further research modeling the cost effectiveness of current and future interventions for neovascular AMD.

Semeraro, F., et al. (2014). "Anti-TNF therapy for juvenile idiopathic arthritis-related uveitis." Drug Des Devel Ther **8**: 341-348.

Juvenile idiopathic arthritis-related uveitis is the most common type of uveitis in childhood and one of the main causes of visual impairment in children. The introduction of biological treatment has widened the range of therapeutic options for children with uveitis refractory to standard nonbiologic immunosuppressants. Data from clinical trials suggest that both adalimumab and infliximab have demonstrated effectiveness and safety in open-label studies, although no large, randomized, controlled trials have been reported so far. The role of etanercept in treating juvenile idiopathic arthritis-related

uveitis is not yet well defined. In our experience, anti-tumor necrosis factor therapy has been shown to be more effective than steroids and/or methotrexate in treating uveitis. Up to now, tumor necrosis factor blocking compounds have been reserved for the treatment of the most severe cases of refractory uveitis, and larger prospective clinical trials are required in order to better assess the safety of these new compounds.

Simonini, G., et al. (2013). "Current Evidence of Anti-TNFalpha treatment efficacy in childhood chronic uveitis: A systematic review and meta-analysis approach of individual drugs." Arthritis Care Res (Hoboken).

**Objective.** To summarize evidence regarding the effectiveness of anti-TNFalpha treatments in childhood autoimmune chronic uveitis (ACU), refractory to previous DMARDs. **Methods.** A systematic search between January 2000 and October 2012 was conducted using EMBASE, Ovid MEDLINE, Evidence Based Medicine Reviews-ACP Journal Club, Cochrane libraries, and EBM Reviews. Studies investigating the efficacy of anti-TNFalpha therapy, in children ( $\leq 16$  yrs), as the first biologic treatment for ACU, refractory to topical and/or systemic steroid therapy and at least one DMARD, were eligible for inclusion. The primary outcome measure was the improvement of intraocular inflammation, as defined by the SUN working group criteria. We determined a combined estimate of the proportion of children responding to anti-TNFalpha: Etanercept (ETA), Infliximab (INF), or Adalimumab (ADA). **Results** We initially identified 989 articles, of which 148 were potentially eligible. Twenty-two retrospective chart reviews, and one Randomized Clinical Trial, were deemed eligible, thus including 229 children (ADA n=31; ETA n=54 and INF n=144). On pooled analysis of observational studies, the proportion of responding children was 87% (95% CI: 75-98%) for ADA, 72% (64-79%) for INF, and 33% (95% CI: 19-47%) for ETA. There was no difference in the proportion of responders between ADA and INF ( $\chi^2$  3.06,  $p=0.08$ ), although both showed superior efficacy compared to ETA (ADA vs ETA  $\chi^2$  =20.9,  $p<0.001$ ; INF vs ETA  $\chi^2$  =20.9,  $p<0.001$ ). **Conclusion.** Although randomized controlled trials are needed, the available evidence suggests that INF and ADA provide proven similar benefits in the treatment of childhood ACU, and they are both superior to ETA. (c) 2013 American College of Rheumatology.

Simonini, G., et al. (2014). "Does switching anti-TNFalpha biologic agents represent an effective option in childhood chronic uveitis: The evidence from a systematic review and meta-analysis approach." Semin Arthritis Rheum.

**OBJECTIVE:** To summarize the evidence regarding the effectiveness of switching to a second anti-TNFalpha treatment in children with autoimmune chronic uveitis (ACU), refractory to the first course of anti-TNFalpha treatment. **METHODS:** We conducted a systematic literature review between January 2000 and May 2013 to investigate the efficacy of a second anti-TNFalpha agent in the treatment of ACU in children ( $\leq 16$  years) refractory to a first course of a single anti-TNFalpha treatment, topical and/or systemic steroid therapy and at least one DMARD. The primary outcome measure was

the improvement of intraocular inflammation, as defined by the SUN working group criteria, at 6 (+/-2) months of treatment. RESULTS: Among 1086 identified articles, 128 were scrutinized: 10 observational studies, 6 on adalimumab (ADA), 3 on infliximab (INF), and 1 on both, were deemed eligible. Study cohort included 40 children (ADA = 34 and INF = 6), median age 8 years (range 3-16). Nine were males, 28 females (gender not reported in 3), 39/40 were affected by JIA. Seventeen children received etanercept: 11 were switched to ADA, the remaining 6 to INF. All 23 children who previously received INF were switched to ADA. Altogether, 30 children (24 on ADA, 6 on INF) of 40 responded to treatment: 0.75 (95% CI: 0.51-100) was the combined estimate of the proportion of subjects improving. CONCLUSIONS: Despite the fact that no RCT is available and the number of cases is small, this review provides evidence that switching to a second anti-TNFalpha agent results in improvement of ocular activity for the 75% treated children.

Simonini, G., et al. (2013). "Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach." Rheumatology (Oxford) **52**(5): 825-831.

OBJECTIVE: To summarize evidence regarding the effectiveness of MTX in the treatment of childhood autoimmune chronic uveitis (ACU). METHODS: A systematic search of articles between January 1990 and June 2011 was conducted using EMBASE, Ovid MEDLINE, Evidence-Based Medicine Reviews-ACP Journal Club, the Cochrane Library and EBM Reviews. Studies investigating the efficacy of MTX as a single immunosuppressant medication in the treatment of ACU refractory to therapy with topical treatment and/or systemic treatment in children ( $\leq 16$  years) were eligible for inclusion. The primary outcome measure was the improvement of intraocular inflammation, expressed as Tyndall, as defined by the Standardization of Uveitis Nomenclature working group criteria. The effect measure for each study was the proportion of people classified as responders. We determined a combined estimate of the proportion of children in the eligible studies responding to MTX. RESULTS: The initial search identified 246 articles of which 52 were potentially eligible. Nine eligible articles, all retrospective chart reviews, remained in the analysis. The number of children in studies ranged from 3 to 25, and the dose of MTX varied from 7.5 to 30 mg/m<sup>2</sup>. Altogether, 95 of 135 children responded to MTX. The pooled analysis suggested that MTX has a favourable effect in the improvement of intraocular inflammation: the proportion of responding subjects was 0.73 (95% CI 0.66, 0.81). CONCLUSION: Although randomized controlled trials are needed, the available evidence supports the use of MTX in the treatment of childhood ACU: approximately three-quarters of patients on MTX can expect improvement in intraocular inflammation.

Thorne, J. E., et al. (2007). "Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss." Am J Ophthalmol **143**(5): 840-846.

PURPOSE: To estimate the incidences of ocular complications and vision loss in patients with juvenile idiopathic arthritis (JIA)-associated uveitis, to

describe risk factors for vision loss, and to describe the association between therapy and complications and vision loss. DESIGN: Retrospective cohort study. METHODS: setting: Single-center, academic practice. study population: A total of 75 patients with JIA-associated uveitis evaluated between July 1984 and August 2005. procedures: Clinical data on these patients were analyzed. outcome measures: Occurrence of ocular complications and visions of 20/50 or worse and 20/200 or worse. RESULTS: Over a median follow-up of three years, the incidence of any ocular complication was 0.33/eye-year (EY). Rates of vision loss to 20/50 or worse and 20/200 or worse were 0.10/EY and 0.08/EY, respectively. Risk factors at presentation for incident vision loss included presence of posterior synechiae, anterior chamber flare  $\geq 1+$ , and abnormal intraocular pressure (IOP). During follow-up, ocular inflammation  $\geq 0.5+$  cells was associated with an increased risk of visual impairment (relative risk [RR] = 2.02, P = .006) and of blindness (RR = 2.99, P = .03). Immunosuppressive drug therapy reduced the risk of hypotony by 74% (P = .002), epiretinal membrane formation by 86% (P = .05), and blindness in the better eye by 60% (P = .04). CONCLUSIONS: Incident vision loss and complications were common. Presence of posterior synechiae, anterior chamber flare  $\geq 1+$ , and abnormal IOP at presentation were associated with vision loss during follow-up. Use of immunosuppressive drugs reduced the risk of some ocular complications and of blindness in the better-seeing eye.

Woreta, F., et al. (2007). "Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis." Am J Ophthalmol **143**(4): 647-655.

PURPOSE: To describe the frequencies of and risk factors for ocular complications and poor visual acuity at presentation in a cohort of patients with juvenile idiopathic arthritis (JIA)-associated uveitis. DESIGN: Cross-sectional study. METHODS: setting: Single-center, academic practice. study population: Seventy-five patients with JIA-associated uveitis were evaluated between July 1984 and August 2005. observation procedures: Data on patients diagnosed with JIA-associated uveitis were entered retrospectively into a database and analyzed. outcome measures: Visual acuity of 20/50 or worse or 20/200 or worse, and presence of ocular complications (including cataract, posterior synechiae, band keratopathy, elevated intraocular pressure, hypotony, macular edema, and epiretinal membrane) at presentation. RESULTS: At presentation, ocular complications were seen in 67% of eyes affected by JIA-associated uveitis. Presence of  $\geq 1+$  anterior chamber flare, a positive antinuclear antibody (ANA), and a shorter duration between the diagnosis of arthritis and uveitis were significantly associated with the presence of ocular complication. The frequencies of 20/50 or worse and of 20/200 or worse visual acuities at presentation in affected eyes were 36% and 24%, respectively. The presence of  $\geq 1+$  anterior chamber flare and a history of intraocular surgery before presentation were significantly associated with 20/50 or worse and 20/200 or worse vision. Presence of posterior synechiae also was associated with 20/200 or worse vision at presentation. The main causes of poor vision at presentation for affected eyes and better-seeing eyes were cataract, band keratopathy within the visual axis,

and glaucoma. CONCLUSIONS: Ocular complications and poor vision at presentation were common in our patients with JIA-related uveitis.

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