NHS England

Clinical Commissioning Policy: Infliximab (Remicade) and Adalimumab (Humira) As Anti-TNF Treatment Options For Adult Patients with Severe Refractory Uveitis

Reference: NHS England D12/P/b

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Infliximab (Remicade) and Adalimumab (Humira) As Anti-TNF Treatment Options For Adult Patients with Severe Refractory Uveitis

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Contents

Policy Statement

NHS England will commissioning Infliximab and Adalimumab for uveitis in adults 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. The conditions are uncommon and at their most severe only affect about 1 in 10,000 of the population. Uveitis accounts for around 10% of visual impairment registrations.

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). The drugs in standard use across the world include prednisolone (steroids) and immunosuppressant drugs. These work in over 60% of patients. However for the remainder of patients these drugs do not work or the patients suffer serious side effects to the drugs that prevent them from being used to their full potential.

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 Inflximab or Adalimumab) is now the standard of care for severe cases across the world.

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.

Patients eligible for treatment with Adalimumab and/or Infliximab are:

- Patients not eligible for admission to a clinical trial for treatment of their uveitis and
- Patients whose condition has proved to be unresponsive to standard treatment
- Patients who are clinically unable to continue with standard treatment because their overall general health is being put under irreversible harm
- Patients who have severe, aggressive disease with risk of rapid, permanent and profound vision loss early in their disease

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.

Over the last 30 years, increasing published evidence and patient engagement (in the UK through the Uveitis Information Group and Birdshot Uveitis Society) has led to a global consensus that drug-induced disease remission needs to be maintained with systemic corticosteroid doses below 10mg prednisolone daily (Jabs et al 2005). To achieve this, conventional second-line immunosuppressive drugs (eg.,methotrexate, mycophenolate mofetil, azathioprine, cyclosporine A and tacrolimus) (Lyon et al. 2009) have been employed, and using harmonised reporting systems this has created a substantial evidence base, despite their off label use. However, around a third of patients still fail to achieve therapeutic remission as defined by SUN (Teoh et al 2008, Hogan et al 2007, Lee et al 2012, Murphy et al 2005) This is also demonstrated in the data from the SITE (Systemic Immunosuppressive Therapy for Eye diseases) cohort study funded by the National Eye Institute. This is a large retrospective study with 17, 316 person years of exposure to immunosuppressive drugs for ocular inflammation and is one of the most formative data series in this disease (Kempen et al 2009).

It should also be noted that in uveitis, the use of systemic corticosteroids is often in high doses for long periods of time (Howe et al 1994; Nguyen et al, 2011). This is shown to cause a number of dermatological (fragile skin, hirsutism, facial erythema, impaired wound healing, striae etc) haematological (increase in total white blood count and promotion of coagulation), endocrine and metabolic (growth suppression, fluid retention, inhibition of the immune system, changes in the electrolyte balance, weight gain, steroid-induced diabetes mellitus), musculoskeletal (osteoporosis) and gastrointestinal (peptic ulcer disease, candidiasis, and pancreatitis) problems (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). Therefore, the minimum dose necessary to control the disease should be given and prolonged use avoided.

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), and this has led to monoclonal antibody therapies against anti-TNF alpha becoming the standard of care in the treatment across the world of those refractory patients whose disease

either remains uncontrolled or who fail to achieve a 10mg dose-threshold of corticosteroid-induced disease remission despite conventional immunosuppression (see evidence summary below) .

2. Definitions

Uveitis: Uveitis is the term used to describe inflammation of any structure within the eye. This policy is for patients with sight threatening and visually disabling uveitis which represents a minority of cases and is typically chronic, persisting for more than 5 years.

I**nfliximab**: 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-TNFalpha 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 adults.

The objectives are to:

- Clarify how the evidence and its quality determine the clinical commissioning position of NHS England for iInfliximab and Adalimumab to treat uveitis in adults.

4. Epidemiology and needs assessment

The prevalence of uveitis is approximately 115.3/100,000 and the incidence is approximately 52.4/100,000 (Gritsz & Wong 2004). It is estimated that uveitis accounts for up to 10% of prevalent blindness in European and North American population-based cohorts and is a significant public health problem (Suttorp-Schulten and Rothova 1996) with significant impact on quality of life (Murphy et al 2005, 2007). Of all patients with Uveitis in England we estimate 20% will have sight threatening disease requiring systemic therapy. Of these 60% treated will respond to standard immunosuppressant drugs including calcineurin inhibitors and anti-proliferative agents in combination with low-dose corticosteroids.

Of the 40% that do not respond to the above treatment, further escalation of treatment is available, prior to biologic use. This includes combining conventional 2nd line agents and using sub optimally high doses of corticosteroids. The remaining 10% who remain unresponsive, estimated at around 220 new patients per annum in England will have ocular inflammation that will fulfil the eligibility criteria of the

clinical commissioning policy for treatment with Infliximab or Adalimumab. This matches the experience of current use through IFR and clinical trial recruitment.

Recent data shows that persistent non-infectious uveitis is associated with substantial direct and indirect costs. Adjusted total direct (c £21,000 vs c £4,600) and indirect (c £4,000 vs c £928) costs were significantly higher for cases vs controls (ARVO Abstract 5320 2014) as well as patients having higher risk of complications and visual disability. Adjusted analysis showed persistent cases had hazard rates that were 8.9, 8.1, 6.2, and 4.2 times higher than controls for any complication, visual disturbance, cataract, and glaucoma, respectively (ARVO abstract 6032, 2014).

5. Evidence base

An evidence review carried out to evaluate the clinical effectiveness, safety and cost effectiveness of the anti-TNF agents Infliximab and Adalimumab in adult patients with idiopathic uveitis and uveitis associated with systemic diseases identified 3 Adalimumab studies (2 open label trials and 1 case series) meeting the inclusion criteria and none for Infliximab.

From the published literature currently available, there is some evidence that Adalimumab helps reduce uveitis flares in patients with anterior uveitis associated with ankylosing spondylitis (Scottish Intercollegiate Guidelines Network -SIGN level 2+, grade D). Evidence of clinical effectiveness in patients with sarcoidosis and other aetiologies of uveitis comes from a small sample case series and an open label study respectively (SIGN level 3, grade D and SIGN level 2-, grade D). No studies for infliximab were found. Well-designed studies are needed and are ongoing to establish the accepted level of evidence for clinical efficacy, safety and cost effectiveness ofInfliximab and/or Adalimumab in adults with idiopathic uveitis and uveitis associated with systemic diseases.

Levy et al (2014) undertook a study to provide recommendations for the use of anti-tumor necrosis factor α (TNF-α) 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 spondyloarthropathy, 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.

A retrospective study of data from a multicentre ocular inflammation biologics registry which included patients capturing routine clinical therapy and disease states in uveitis within the United Kingdom was undertaken. Patients >18 years who were given either adalimumab (40 mg/2 week) or infliximab (3-5 mg/kg/2 weeks) were included. Details of the methodology and analysis are provided in appendix 3. The following key results were reported:

- All patients (n=41) on biologics showed clinical remission after a mean (± SD) follow-up of 1.36(± 0.88) person years.

- Higher proportion of patients (48.78%) showed improvement in visual acuity as compared to patients (17.07%) showing worsening in visual acuity after a mean (± SD) follow-up of 2.51(± 2.01) and 4.38 (± 3.50) person years, respectively

- 88.89% of patients on biologics showed reduction in steroid dose to ≤10 mg, followed by 75.85% of patients showing reduction in steroid dose to ≤5 mg, and 45.16% completely stopping Prednisolone use after a mean (± SD) follow-up of 3.06 (± 2.32), 3.15 (± 1.76), and 3.49 (± 1.59) person years, respectively.

- 83.33% of patients on biologics showed reduction in the number and/or use of IMT after a mean (± SD) follow-up of 1.54 (± 0.99) person years.

- The median vision-related quality of life (VCM) scores decreased as the follow-up time after the start of biologics increased.

- The mean SF-36 PCS scores were below the average range (<47) for the general population. With the exception of the SF-36 MCS scores at 3 years, the SF-36 MCS mean scores were above the average range (>47) for the general population.

- The vision-related quality of life (VCM) scores significantly decreased with decrease in visual acuity scores of worse eye within 1 year of starting biologics (p=0.0064).

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, Japan.

Evaluating the success of anti-TNF alpha treatments in uveitis to level 1 evidence will require clinical research. There are large-scale trials currently underway and are yet to report.

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.

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).

Testimonies from patients 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 immunosupresants and long-term steroid use and the positive impact and 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

Infliximab/Adalimumab in ocular inflammation

Access to Adalimumab and Infliximab would be provided through specialised Uveitis networks with access to nationally or internationally 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.

Infliximab or Adalimumab will be used to treat Uveitis in patients who fulfil the following criteria:

- The patient is not eligible for admission to a clinical trial for treatment of their uveitis
- Patients whose condition has proved to be refractory to treatment (as per SUN guidelines) despite supramaximal treatment with more than 10mg/day of prednisolone and at least two immunomodulatory drugs (e.g. Tacrolimus and Mycophenolate mofetil)
- Patients who are clinically unable to continue the above treatments because of severe intolerance or toxicity, i.e. their overall general health is being put under irreversible harm or the drugs are contra-indicated.
- Patients who manifest severe, aggressive disease with risk of rapid, permanent and profound vision loss early in their disease (eg Retinal Vasculitis); similar to agreed national commissioning guidelines for Behcet's disease (reference)

Patients who satisfy the eligibility criteria will be prescribed Anti-TNF treatment (Adalimumab or Infliximab) following consultation with the patient and/or carer taking into account:

- Suitability of the drug, i..e Adalimumab, Inflximab
- Delivery method of the drug (see below)
- Potential adverse effects and contraindications

Where all other considerations are equal, the drug with the lowest acquisition and delivery cost will be used.

The recommended Adalimumab treatment dose regimen for adults with ocular inflammation is 40 mg every other week via self-administered subcutaneous injection.

The recommended Infliximab treatment dose regimen for adults with ocular inflammation is induction at 0, 2, and 6 weeks at a dose of 3–5 mg/kg. Thereafter, it is given every 4–8 weeks at a dose of 3–10mg/kg. It is given in hospital by intravenous infusion.

Patients will be regularly monitored at a minimum of three monthly intervals by the specialised centres.

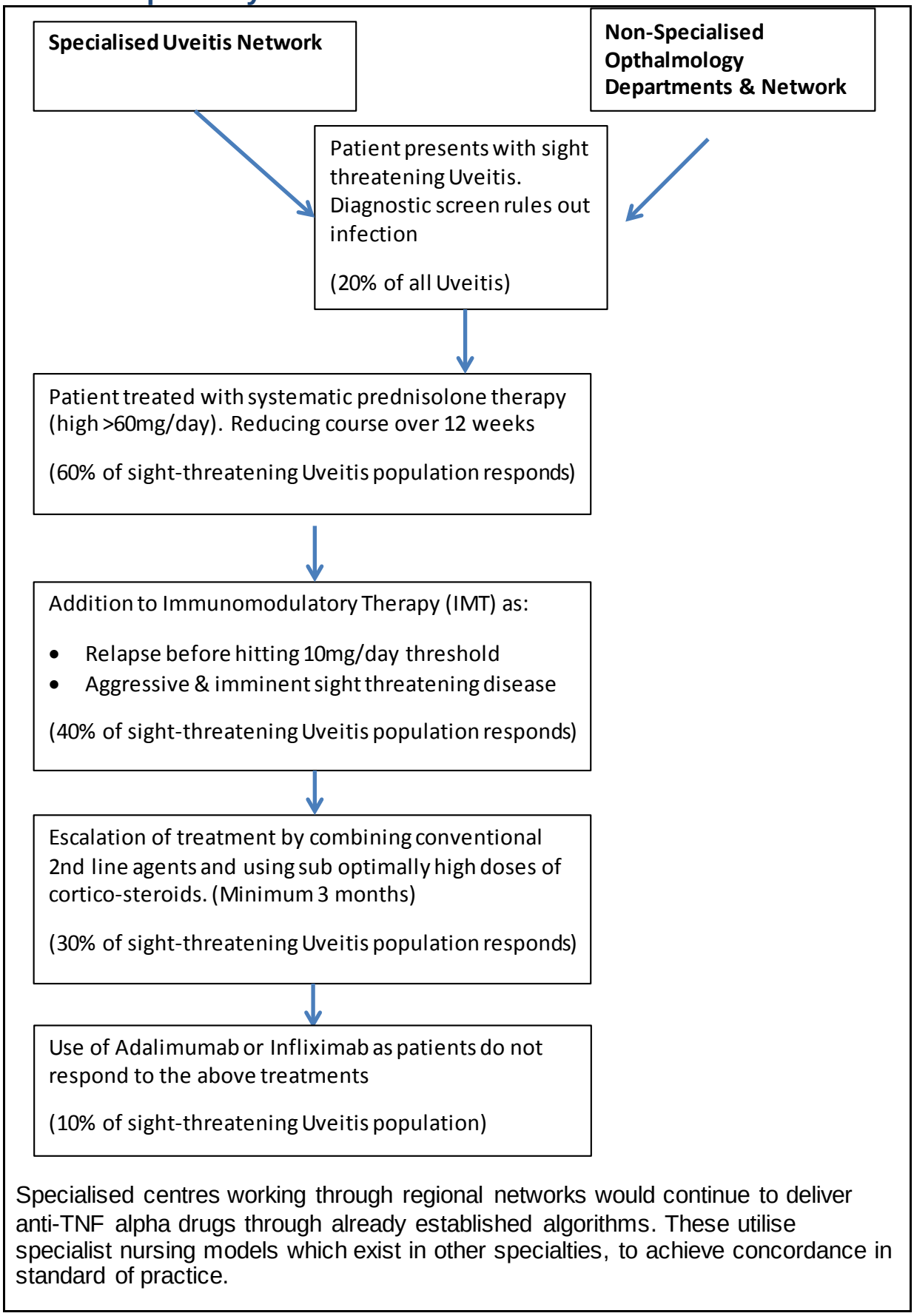
Stopping criteria

Treatment with Adalimumab or Infliximab will be stopped using the following criteria:

- There is no benefit from treatment after 3 months of treatment being initiated.

Patients who respond and achieve drug induced disease remission will continue therapy for up to 2 years. After 2 years therapy will be withdrawn. If there is disease relapse, restarting anti-TNF therapy will be considered.

8. Patient pathway



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.

9. Governance arrangements

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

Adalimumab or Infliximab should not be used unless a patient has failed optimised treatment for at least 3 months (see sections 4 & 8 above).

The optimum therapy will be individually chosen by the consultant ophthalmologist following full discussion with the patient, carers (if appropriate), and the specialist multidisciplinary team (MDT).

All patients who commence treatment with Adalimumab or Infliximab should be enrolled 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

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 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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APPENDIX ONE – PATIENT TESTIMONIES (ADULT)

This section was added following comments received from CPAG 1st October 2014.

Introduction

The following are patient testimonies written by patients who have been prescribed Anti-TNF alpha treatments. The patients have given their permission for these testimonies to be used in support of the proposed commissioning policy for the use of Anti-TNF alpha treatments for adult patients with severe refractory Uveitis. Where patients are named they have given their specific permission. The words are the patient's own.

Testimony #1

NAME: REA MATTOCKS

DATE OF FIRST SYMPTOMS: SEPTEMBER 2005

DATE OF DIAGNOSIS: JANUARY 2006

DIAGNOSIS: BIRDSHOT CHORIORETINOPATHY; A RARE, POTENTIALLY BLINDING, AUTO-IMMUNE FORM OF POSTERIOR UVEITIS

In September 2005, whilst working as Director of Social Services for a large county council, I woke up one morning with a mist across my eyes.

Whilst walking into my office, I fell down the stairs, as I could not judge the depth of the stairs. I also could not read my emails or paperwork. This prompted me to see an optician who immediately referred me to eye casualty. Throughout my working life, I had never had even a single day off in sickness, so was very unprepared for what was about to happen.

At eye casualty, I was reassured that I had age related Posterior Vitreous detachment, and that it would settle. However, my vision continued to deteriorate to the extent that I could no longer see anything in front of me.

I returned to the hospital on 7 October 2005 and was referred to a consultant, who immediately started me on oral steroids (prednisolone) whilst embarking on a range of tests to find the cause of the inflammation.

Despite high doses of steroids (35 mg – my weight was 45 kilos) my vision continued to deteriorate and In January, 2006, I was diagnosed with Birdshot Chorioretinopathy and started on high doses of mycophenolate mofetil (1 gm bd) alongside steroids.

This combination stabilised my vision deterioration, but only at high doses of steroids, and had disastrous consequences for my work and home life and on my mental health and well-being. Within a short period of time, I developed osteopenia and became quite irrational, experiencing periods of highs and lows. I rarely slept, and terrorized my staff, as well as acting inappropriately in committee meetings. I gained 2 stone in weight, had skin lesions, increased heart rate, cushings syndrome, short term memory loss and was constantly ill with infections. I had also managed to alienate family and friends with my behaviour, as well as work colleagues.

My job was at risk from my behaviour, my constant illness and my inability to see. The last thing I wanted was to have to give up work and become an un-productive member of society, whilst also facing the possibility of losing my vision, so I became extremely depressed, and started exploring ways in which I might be able to end my life.

My consultant suggested that, given my intolerance to steroids and immunosuppressants, an application should be made to the PCT for an anti-TNF, adalimumab. This medication had a good track record with people suffering from rheumatoid arthritis, and there was quite a large body of anecdotal evidence to suggest it was very helpful in cases of people with auto-immune posterior uveitis who were intolerant of conventional immunosuppressive regimes. I sought a private second opinion at Moorfields who also recommended an application for adalimumab. The application was submitted in September 2007.

The application pointed out the health economic arguments such as the cost of adalimumab versus the costs of the current regime and the continuing cost to the health and social care budgets as I lost sight, experienced fractures due to osteoporosis and started to use mental health services for my depression and memory loss. It also pointed out that no drug was specifically approved for, or licensed for Birdshot Chorioretinopathy, as this is a rare disease.

The application was turned down in November 2007 on the grounds that 'the proposed treatment has not been licensed to treat Birdshot Chorioretinopathy', 'there is limited evidence to support the use of this treatment' and 'there was no evidence of alternative immunosuppressive regimes being used'.

I LOST MY JOB!

An appeal was submitted, and funding was finally approved in May 2008.

Once on adalimumab, my visual acuity began to improve (for the first time since I was diagnosed with Birdshot), and I was able to dramatically reduce the steroids and mycophenolate mofetil.

Adalimumab was the ONLY medication able to control the Birdshot. Too late to save my job, too late to save me from osteopenia and a large amount of visual loss. Too late to save some of my relationships with friends and family members. But it has returned some of my vision, and stopped me from wanting to take my life.

I believe that the health economic argument for using anti-TNFs in patients who are resistant to conventional immunosuppressive regimes, except at high doses is indisputable. Had I been prescribed adalimumab earlier, I would still be earning and contributing in the form of taxes to our society. I would not need the constant monitoring of my bones, nor would I need the use of resources for any fractures. I would not have needed the cataract operations and the subsequent ptosis correction. I would not have needed to waste precious NHS resources on trying a range of alternative expensive immunosuppressive regimes that did not work. I would be able to see better and not be a drain on our health and social care systems.

The direct cost of Anti-TNF alpha treatment is more expensive than that of systemic corticosteroids, however these costs diminish when other costs such as loss of

earnings (tax revenue and National Insurance, including employer's contribution) from both patients and carers, benefit costs (employment & support allowance, welfare benefits, personal independence payments, mobility payments, carers allowance, carers credit, TV license, blue badge scheme, concessionary public transport travel, reduction in council tax, housing benefit, other social care costs, including aids to daily living, adaptions to home etc, and attendance allowance are added. These costs, when added to the costs of systemic corticosteroids are estimated at, at least £55,000 per annum, and will be for life, whereas a patient receiving Anti-TNF treatment is likely to continue to be able to work and the intervention is for around 2 years.

Testimony #2

Having spent over 3 difficult and stressful years struggling to contain a progressive eye disease through different combinations of steroids and other immunosuppressant drugs, Richard Lees & his team were able to gain me access to the biologic Humira. This drug has made a massive difference both to the eye disease and to my general wellbeing (Humira is also working in combination with Methotrexate to control my Rheumatoid Arthiritis).

It's difficult to explain and express the fear and worry of having a 'rare' eye condition which if left untreated will deteriorate to potentially losing my eyesight. The stress and feeling of helplessness & vulnerability is amplified with the knowledge that there is a potential drug treatment that is not normally available .

Thankfully in my case access to the biologic Humira was granted. This has had an immediate and positive impact on my eye condition and my wellbeing. It's given me back the confidence and reassurance of a 'normal' life without the worry and anxiety of a deteriorating eye disease. In addition, not only has the quality of my life improved but it has also resulted in much less frequent trips to the Bristol Eye Hospital - saving time, money and energy, as well as allowing other drugs to be reduced or stopped entirely. Surely a positive for all involved, patients & the hospital.

Access to Humira has changed my life, and I am very grateful for everyone involved in enabling it to be granted for my treatment.

BK

Testimony #3

I am under the care of the MIN (Royal National Hospital for Rheumatic Diseases) in Bath. My previous treatments were failing, and on the advice of Professor Dick, Humira, was proposed, both to save my sight as a matter of urgency, and to combat spinal displacement and overall pain and swelling.

The result of this and subsequent biological drugs have stabilised my sight and allowed me to live a fuller and less painful life. To expand I have a little more energy, I can continue to drive to a limited extent. Although I still have problems doing things with my hands and walking I think that I am less of a burden on my wife. Now that I only have to attend the hospital for programmed visits rather than in haste when having an emergency or for many weeks following an crises situation it much less

stressful and draining for both my wife and myself. The work at the eye hospital has been well received and acted upon by the Min.

I am truly grateful for the care that I am receiving as it has given me a quality of life and reduced the burden on others which can't be bad.

DH

Testimony #4

I was first prescribed Humira in November 2010 following eighteen months of intensifying pain and anxiety about my eyes. For most of this period I kept a pain diary, and was regularly at 9/10 (pain so severe I was disorientated) and rarely below 6/10 (nearly bearable). My life revolved around eye hospital appointments; I went twice to the Eye Hospital's A&E and had several inpatient cycles of IV prednisolone. The effect of all this on my quality of life was profound; I also had to stop working, which caused financial difficulties and diminished my self-esteem.

The process of working through other drug options before being prescribed Humira was awful. Oral methotrexate and Cellcept both made me nauseous without noticeable benefit; I went through several cycles of reducing prednisolone before it became apparent that they were only effective at doses which I couldn't tolerate because of psychological side effects. In the summer and autumn of 2010 it was so difficult to cope that I ate the same (healthy but dull) dinner for weeks, because it minimised effort and meant I didn't have to think. The repeated experience of unsuccessfully trying different medications was dispiriting to the point of hopelessness.

After having watched and recorded my pain for so long, I knew within a few days of first using Humira that it was having an effect: there was a corresponding benefit to my mood and to my ability to cope generally. Since increasing the dose from fortnightly to weekly my scleritis has stabilised. My pain score is generally (with painkillers) between 0/10 and 3/10. I have started working again, and although my life is still dominated by the medication cycle, the side effects now are generally moderate fatigue and occasional nausea (reduced by changing to injections of methotrexate). I've (more or less) learned to cope.

When I come into the Eye Hospital now, I no longer feel afraid of the place or the 'system': I feel I'm a 'participant' as well as a patient . This has been very important in helping me to come to terms with very difficult changes to my capabilities.

BS

Testimony #5

I have been a patient of Professor Dick's for many years and have benefited enormously from treatment with firstly infliximab and currently adalimumab.

Suffering from uveitis, my eyesight continued to deteriorate even though I was taking a combination of prednisolone, cyclosporin and mychophenolate. Each drug had its own side-effect, none of which were particularly pleasant. The dose of steroids was increasing and I was very keen to try the biologic treatment.

Thankfully, Professor Dick applied for and was granted funding for my biologic treatment. Since then, I have been able to stop taking both the mycophenolate and the cyclosporin and I have reduced the steroid dose to a very manageable level.

The benefits of the treatment to me personally have been great. My eyesight has stabilised and I am able to lead a normal life. Only those threatened with the fear of blindness can truly appreciate the miracle of sight and its fundamental role in allowing us to live our lives normally and without dependence on anyone else.

What is potentially more important is the considerable saving to the economy as a whole in that I have been enabled to continue in full time employment and will be able to continue doing so whilst I am on the biologic treatment. Consider the effect on the economy if every patient who could benefit from the drug was given access to it, immediately and without the battle to receive it. Every individual would be able to continue in the workforce, independent of the state.

ED

Testimony #6

Before starting on this therapy I felt I was going from one flare-up to the next, making my life very unpredictable. For some time I was very fearful not only of losing my eyesight but of losing my independence entirely.

I already have mobility difficulties following a work accident in my 20's but despite my problems with this I have always maintained a good work record of which I am very proud. The idea of being unable to work was unbearable to me and left me feeling low spirited and fearful of my future.

My uveitis is bilateral, so when my eyesight became poor quite quickly my driving licence was taken away from me. I could not use public transport on my own as I could not safely cross the busy roads or read the bus numbers. I worked from home when I could or my employer paid for a taxi to and from work when needed. Other than this I was virtually housebound, in my early fifties, and did not know how I would face my future.

In addition to this I was losing my ability to keep my interests, hobbies and volunteer activities, all of which have been an important part of my life not only to distract myself from the pain caused by my earlier accident, but to express myself and to feel I could function as a contributing member of society and my local community.

My life at home became difficult too as a lot of the time I was unable to perform my usual tasks and became more and more reliant on my husband.

I felt that the combination of losing my role at home, at work and with my voluntary activities meant the end of my independence and my identity, which is surely a serious loss to face.

Since I have been established on the Biologic therapy I have been so much better. I feel my life is stable and predictable, and I can carry on working and contributing for [I hope] many more years to come. My eyesight now is just about perfect and I can see as well as I could before I had the uveitis.

I am busily working, still volunteering, and feel really grateful that I have been offered this chance to have my life given back to me.

GC

Testimony #6

As a patient representative on the CRG I strongly support making anti- TNF treatments available to patients who do not respond to traditional treatment. As a two year old I was diagnosed with uveitis which was uncontrolled for some time. This resulted in macula damage to one eye and glaucoma in both. The glaucoma was also difficult to control and resulted in a number of glaucoma operations, life-long medication and sight loss. One eye also developed corneal dystrophy from the complications of uveitis and now has light perception only. The uveitis eventually abated but the resulting complications remain. I am now registered as partially sighted due to the damage from the macula oedema and glaucoma. For glaucoma I have recently undergone specialised surgery which has required intense follow up for over a year. I will also have a second corneal graft later this year.

Effects on life

My poor vision means that my career is limited and I cannot drive or find my way around outdoors without difficulty. I also need to attend regular hospital appointments which means I have to take time off from work. I also need to live in an area which is close to specialised services to limit the impact of the hospital appointments on my daily living.

As a child my frequent follow up appointments and operations impacted on my parents and carers who needed to take time of work to attend.

Conclusion

Had this treatment been available to me as a young child I might have avoided some or all of the complications I now suffer from uveitis. No doubt the cost of the complications has far outweighed any initial cost for the anti -TNF treatment, even without considering the massive impact that this has had on my life.

Testimony #7

I wish to convey to you how much Infliximab has changed, not only my life for the better but that of the NHS as well. I started to lose my eyesight at the age of 17, and the years that followed were the most unpleasant of my admittedly short life. I was placed on high dosage of prednisolone steroids along with Cellcept, Tacrolimus as

well as a host of eye drops. All of which resulted in extreme mood and behavior swings. My Mother who loves my very much described me "Dr Jekyll and Mr Hyde" during this period. My behavior was such that a group of fellow students asked me to leave our shared accommodation while I was studying at Swansea University.

On top of the psychological impact such medications brought and the real life social impact it was having, I was also in and out of hospital and back and forth to the GP surgery due to a near constant state of illness and a seemingly never ending string of infections. All of which culminated in me having to leave university before my degree was completed.

The reason I tell you these details is as a result of being placed on Infliximab I am no longer on prednisolone steroids, I am no longer on Tacrolimus and my Cellcept intake has been halved. My bouts of illness have decreased to a point that I am maybe no more bedridden with sickness than your average healthy person. I am not back and forth to the GP or taking up a valuable bed in a ward. Most importantly off all my mental state has stabilized and my bouts of aggressive behavior have ceased. Because of Infliximab my eyesight is no longer at risk and my world is stable enough to make plans for my future. I hope you give others that stability and hope as well.

AJR

The following are words of patients provided by Olivia's Vision, a charity established to help reduce the fears and anxiety felt by patients with a diagnosis of Uveitis. These are excerpts from a minute number of emails and website forum questions.

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

Ease of Access of Biologics via rheumatology

I am only on anti inflammatories and pain killers normally. I am still on the steroids for my eyes at the moment so unsure if these will be continued. I am waiting for an appointment with my rheumatologist to discuss what has happened recently as well as seeing the eye consultants this Friday. I have been offered biological therapy but as I am hoping to start trying for a family this year they have advised I should start the treatment after children.

Intolerance of immunosuppressants, side effects described*:*

… so then followed my foray into the world of immunosuppressants. On Methotrexate I felt like I'd been run over by a bus. On Azathiaprine – I threw up every day.

Finally Moving on from high dose oral steroid, but too late to save sight

After a year on 60mg of steroids and various attempts to taper, to no avail without another raise in inflammation - I have started immunosuppressant treatment to try and put me in remission, I am only 2 weeks into the course of treatment so early days and fingers crossed. I am terrified that I will end up losing all my sight (I now have a certificate of severe sight impairment), driving license now gone too.

Complications

Glaucoma Drops

I was given Diamox intravenously and then put on Diamox tablets for 2 weeks with Cosopt Eye drops. The Diamox made me incredibly ill the point where I never want to go on them again. I was like a zombie.

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.

Cataracts and Glaucoma

The frequent use of Pred Forte caused Cataracts, these were removed from both eyes 3 years ago. Glaucoma was my next visitor, it came so quickly - even though I was monitored very regularly, "spikes" of increased pressure caused considerable permanent vision loss to my right eye - I had to have an emergency operation to have a "bleb" drain inserted in my eyeball to prevent further damage, 3 months later this occurred in my left eye requiring a "bleb" to that eye too

The impact of uveitis on everyday life AND the need for counselling.

Fear of blindness

Sorry if I sound like I'm hyperventilating but I wanted to get it all out as I am increasingly concerned that I need to change my career path and don't want to cause any permanent damage to my vision whilst people are trying to get the condition under control.

Job at Risk

I have had lots of time off work; I am a Data Manager in a high school, so the nature of the job is very stressful and at times impossible to do when my condition is at its worst. It is difficult to do a job on a computer when all you can see is fog and floaters. It seems to be never ending and I am finding it increasingly difficult to remain positive when each treatment fails me.

APPENDIX TWO – Cost effectiveness

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 (1st 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 unreferred 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 immunosupressants 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 75x0.44=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 75x £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 35x £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.

Health state	**Good prognosis**	**Poor prognosis**
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 patients 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 centres on whether a 10 or 20% risk of heart disease over ten years in 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.

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 </=20/50, 144 eyes (24.2%) had a VA of </=20/200, and 359 eyes (60.2%) had at least 1 ocular complication.

The incidences of VA loss to the </=20/50 and </=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 </=20/50 and </=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 </=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 < or =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 <or= .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 <or= .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 >/=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 spondyloarthropathy, 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 (</=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 (chi2 3.06,p=0.08), although both showed superior efficacy compared to ETA (ADA vs ETA chi2 =20.9, p<0.001; INF vs ETA chi2 =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 (</=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 (</=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/m2. 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 > or = 1+, and abnormal intraocular pressure (IOP). During follow-up, ocular inflammation > or = 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 > or = 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 > or =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 > or =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.