Interim Clinical Commissioning Policy: Adalimumab for Children with Severe Refractory Uveitis

Reference: D12X02
NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.

NHS England’s previous policy of not routinely commissioning Adalimumab for Children with Severe Refractory Uveitis was set out in commissioning policy reference D/12/P/b dated July 2015 and this policy is superseded in so far as it relates to the commissioning policy for Adalimumab for this indication; the current version of D/12/P/b dated November 2015 retains a policy for not-routinely commissioning Infliximab (Remicade) as Anti-TNF Alpha Treatment Option for Paediatric Patients with Severe Refractory Uveitis.

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Executive Summary

Policy Statement

NHS England will routinely commission Adalimumab for Severe Refractory Uveitis with onset in childhood (age 2 or more up to 18 or less), in accordance with the criteria outlined in this document. This is on an interim basis until the details of the Sycamore trial are published.

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

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.
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 that is a spectrum of irreversible sight loss affecting both eyes to a level that precludes normal ‘print’ education or driving and includes total blindness.

Uveitis is commonly associated with a variety of inflammatory conditions affecting other organs. In children, Juvenile Idiopathic Arthritis (JIA) is the most common associated disease, where the eyes are affected in a similar way to the joints. In JIA, 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 irreversible sight loss requires drugs that suppress immune cells (the white blood cell that protect us from infection and damage to our tissues) throughout the body. These are associated with significant short and long term side effects.

If conventional immunosuppressants fail, the next step in treatment is the use of a group of drugs known as ‘biologics’. These are very specialised and are designed to target specific molecules released during inflammation from cells and by doing so suppress inflammation.

An evidence review from October 2014 did not find clinical effectiveness had been demonstrated at a high level. Data from a clinical trial, the SYCAMORE study, demonstrating clinical effectiveness of the drug Adalimumab has been made available to NHS England to allow the formation of this clinical policy. The policy will be reviewed when the trial is published.

In this policy children eligible for Adalimumab have sight threatening uveitis (criteria described below in Section 7), and have not shown an adequate response to topical steroid eye drops plus full dose methotrexate (or be intolerant of full dose methotrexate), and otherwise require prolonged high doses of systemic steroids to control 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 and cataract. 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 JIA-associated uveitis is associated with, at first presentation: poor vision (visual acuity less than 6/18); high inflammatory activity; uveitis onset before diagnosis of arthritis; less than 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). Children with idiopathic uveitis, or those with uveitis preceding the diagnosis of arthritis are at an especially high risk of visual loss as they usually present with established structural damage to the eye.

Treatment of Uveitis in Children

The aim of treatment is to prevent or minimise ocular inflammation becoming chronic, and thereby to 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 of uveitis in children is with local therapy (topical steroid eye drops or peri- and intra-ocular steroid injections depending on severity), combined with high dose systemic steroid (either oral or intravenous), if local treatment does not induce remission.
Children with severe features at presentation, or those children in whom uveitis activity increases following reduction of the dose of systemic steroid, proceed to treatment with a second line agent, as the prolonged use of high dose systemic steroid (> 0.1mg/kg/day) is associated with severe side effects involving many organ systems such as (Howe et al 1994) (Stanbury et al 1998):

- 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 (osteoarthritis)
- Gastrointestinal (peptic ulcer disease, candidiasis, and pancreatitis)

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). The minimum doses of topical, periocular and systemic steroid necessary to control the disease should be given, and prolonged use avoided.

If uveitis disease activity cannot be controlled (SUN cells score ≤0.5+) with ≤0.1mg/kg/day systemic steroid, plus ≤ 2 drops of topical steroid eye drops per day, then a second line agent is considered to reduce the complications of long term steroid use.

The standard initial second line agent, for JIA is Methotrexate (MTX). Methotrexate may be given orally or by subcutaneous injection and is often successful in controlling uveitis in combination with low doses of topical and, if necessary, systemic, steroid. Other conventional immunosuppressants are used as the initial agent in other types of uveitis, especially when other inflammatory diseases are present.

In a minority of children, uveitis is not controlled by tolerated levels of systemic and topical steroids combined with a single conventional immunosuppressant.
Prior to the availability of biologic agents, such children were treated with an alternative second line immunosuppressive agents, such as Ciclosporin, Mycophenolate, Azathioprine, Tacrolimus and Cyclophosphamide, or multiple combinations of these drugs. There is little evidence (and no RCT evidence) that these drugs are more effective, in combination than single agents, and none have demonstrable superiority to MTX when used as the initial agent. Their use is associated, especially in combination treatment, with significant systemic side effects.

Anti-TNF agents are antibodies directed against Tumour Necrosis Factor α, a cytokine which has been shown experimentally to be involved in the pathogenesis of uveitis. The currently available anti-TNF agents include Etanercept, Adalimumab, Infliximab, Golimumab, and Certolizumab. Several other classes of biologics have been used in both idiopathic uveitis and the systemic inflammatory diseases with which it is associated and in which there can be other major site of organ damage. These include agents such as tociluzimab and abatacept in JIA, rituximab in systemic vasculitis and, canakinumab in CAPS and Blau syndrome. At the present time there is little evidence of the superiority of any one class of biologics being more effective than another.

Trial data suggests that Etanercept has no impact on disease activity in JIA uveitis, and may in fact provoke the development of 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. Etanercept 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 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.

Children treated for JIA with Adalimumab and Infliximab have been noted to show improvement in uveitis. This has led to their use in the treatment of severe uveitis in children who do not have a diagnosis of JIA, but have JIA-like uveitis of sufficient severity to merit the use of these agents.
The Sycamore trial has now demonstrated benefit to uveitis activity and related complications from the use of Adalimumab. Infliximab has not been evaluated in the same way and there are no comparative trials between the two drugs, although observational studies find little difference in efficacy and it is the standard of care for treatment.

There is no evidence that efficacy of anti-TNF agents is affected by the age of the patient although the safety profiles and side effects may be.

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.

Adalimumab: 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 Aims and Objectives

This policy aims to set out the NHS England Commissioning position for the use of Adalimumab for severe refractory uveitis of childhood onset.

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 (JIA-U)

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. Uveitis is the 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).

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 (affecting both eyes and representing the ‘tip of the iceberg’ of the spectrum of visual disability) in England and Wales is caused by uveitis (Rahi 2013). There are approximately 100 new presentations per annum, with other children visually impaired from complications of uveitis such as cataract and glaucoma.

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 their uveitis is phenotypically identical to JIA-U with the same attendant complications and visual outcomes. There are also patients with uveitis of childhood onset phenotypically identical to those found in adulthood.

Effects of Visual Impairment on Children, their families and society

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. The impact of visual impairment on health related quality of life of children has been shown to be equivalent to that of certain cancers and other serious chronic conditions. For parents and carers of children with severe uveitis, there is the additional burden of multiple hospital attendances with their child and their ability to maintain employment. Permanent sight loss starting in childhood confers lifelong disadvantage in terms of occupational and social opportunities for affected individuals and their families and a significant loss of economic productivity to the communities in which they live.

5 Evidence Base

An evidence review of Adalimumab in paediatric patients with idiopathic uveitis and uveitis secondary to Juvenile Idiopathic Arthritis (JIA) completed in October 2014 identified 4 studies.

Tynjala et al (2008) investigated its use as a third line agent in 20 patients with JIA and chronic anterior uveitis. They reported 35% (7/20) patients had improved activity of uveitis, 60% (12/20) had no significant change and activity worsened in 5% (1/20) and AC flares reduced by 0.5 per year (not statistically significant) at a mean follow up duration of 18.7 months. The study included patients with underlying differences in disease severity, sub-type of JIA, age of onset, duration of the disease and varied follow up. Methotrexate was used as concomitant treatment in the study.

The study by Kotaniemi et al (2011) included 54 patients with JIA and uveitis who were either not responsive to standard immunosuppressive therapy for uveitis or were intolerant to it. In 22/54 patients’ adalimumab was used as a first-line anti-TNF treatment. During a mean follow up of two years, uveitis activity according to the SUN criteria improved in 57% (31/54) of the study patients (31/54). The patients in the study had heterogeneous underlying disease (type of arthritis, age at diagnosis, duration etc), treatment history, had varied treatment frequency and variable follow-up. Concomitant treatment was given to all except 4 patients.

A study by Simonini et al (2013) compared efficacy of adalimumab as a first line anti-TNF-α therapy, versus Adalimumab, used after the failure of a previous anti-TNF α (Infliximab) with 26 patients with uveitis. They were divided into 2 groups- one group (n=14) where adalimumab was first line treatment and a second group (n=12) where
it was used as second line treatment. Of the 26 patients 20 had uveitis associated with an underlying autoimmune disease (17 JIA, 1 early-onset sarcoidosis, 2 Behçet's disease) and 6 had idiopathic uveitis. The study reported better efficacy of adalimumab when used as first anti-TNFα treatment compared to second line use in childhood chronic uveitis in terms of time to achieve remission (12 weeks Vs 16 weeks, not statistically significant), probability of remission (4 ±0.6 Vs 18 ±1.1 months, p<0.002), time to discontinue steroids (7 ±1.7 vs 3 ±0.9 months, p < 0.001), relapse of uveitis (median number of relapse was 0 Vs 2 in the first year if treatment) and visual acuity (improved in 84.5% Vs 17%, p < 0.001). In a sub group analysis limited to patients with JIA, similar improvements were seen in patients treated with adalimumab as first line (probability of uveitis remission p < 0.002 and time of remission on treatment, 6 ±1.2 Vs 19 ±0.9 vs months, p < 0.001). The total median length of uveitis duration before adalimumab treatment was significantly higher in the group who received adalimumab as second line compared to the second line treatment group- 28 months, range 22–34, Vs 16 months, range 12–22 (p = 0.001). Patients included also had underlying differences in the cause of uveitis and severity of disease. Concomitant treatment was also used during the study.

Magli et al (2013) reported the efficacy of adalimumab in 21 patients with anterior uveitis associated with JIA. All patients had oral steroids. 14 were treated with methotrexate and 11 were treated with a different biologic. The study reported improvement in uveitis activity (in 76% eyes), visual acuity (from 20/50 at baseline to 20/32) and flare rate (from 1.6 + 0.4/year to 0.7 + 0.3 per year (p<0.001) at mean follow up of 18.2 +7.7 months. Patients had differences in underlying disease, severity and duration of disease, frequency of treatment and follow up.

In March 2015 a multi-centre clinical trial of adalimumab stopped recruitment. The published results are due to made available in early 2016. Early data has been made available in confidence to NHS England to support the evidence base of clinical effectiveness. The Sycamore trial randomised 85 children with refractory uveitis associated with JIA having treatment with methotrexate to either Adalimumab or placebo. 85 children were randomised (57 to Adalimumab and 26 to placebo). 5 children withdrew from each group. The primary endpoint was time to treatment failure. The trial was stopped early for efficacy after 90 patients had been randomised as interim analysis met the pre-specified stopping guidelines. The final analysis of the
primary outcome showed positive treatment effect in favour of Adalimumab: hazard ration 0.27 (95% CI 0.13-0.52); p<0.0001. The safety profile of adalimumab was consistent with that previously reported.

Treatment failure in the study was defined by ONE or more of the following:

1. Anterior segment inflammatory score grade (SUN criteria) following at least 3 months of therapy:
   - 2-Step increase from baseline in SUN cell activity score (AC Cells) over 2 consecutive readings
   - Sustained non-improvement 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 co-morbidity* which is sustained
   - Worsening of existing (on enrolment) ocular co-morbidity* after 3 months
   - Sustained scores as recorded at entry grade measured over 2 consecutive readings (grades 1 to 2) still present after 6 months of therapy.

2. Use of Concomitant Medications: At any time, requirement to use concomitant medications in manner out with pre-defined acceptable criteria

3. Intermittent or continuous suspension of study treatment (adalimumab/placebo) for a cumulative period longer than 4 weeks

There is currently insufficient evidence to support the treatment of severe refractory uveitis in the absence of JIA with any other biologic.

6 Rationale behind the Policy

There is 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 from experimental medicine studies. The Sycamore trial has demonstrated a benefit from the use of Adalimumab in uveitis associated with JIA.
7 Criteria for Commissioning

Access to Adalimumab must be provided through commissioned specialised paediatric ophthalmology centres with the necessary paediatric rheumatology, consultant ophthalmology and paediatric-trained Clinical Nurse Specialist expertise to oversee treatment decisions falling within this policy.

Start Criteria

Children eligible for the use of Adalimumab for the treatment of uveitis would meet the following criteria:

1. The presence of active anterior uveitis, defined as a sustained grade of ≥+1 cellular infiltrate in the anterior chamber
   AND

2. Failure to control uveitis to +0.5 cells or less with:
   - 0.1mg/kg/day of oral prednisolone in combination with
   - Methotrexate (minimum dose of 10 mg/m² with a maximum dose of 25 mg/m²) and
   - 2 drops of topical steroid eye drops per day.
   - Treatment effect should be assessed after at least 12 weeks.
   - When the patient is methotrexate intolerant an adequate trial (3-6 months) of an alternative conventional immunosuppressant should be given.
   - Exceptionally a child, presenting with very severe sight threatening disease, will be considered for Adalimumab before the end of a 12 week trial of prednisolone and methotrexate.

Very severe sight threatening features at presentation include:

- Severe inflammatory activity (≥3+ cells)
- Cataract
- Glaucoma (Intraocular pressure >21mmHg with evidence of optic neuropathy)
- Hypotony (Intraocular pressure ≤5mmHg)
- Dense vitreous opacity
- Macular oedema causing visual impairment ≤6/18

Patients must be registered with the Blueteq system confirming the start criteria are met. As this is an un-licenced treatment clinicians must follow their employers’ requirements regarding patient/carer consent for treatment.

**In Treatment**

Response to therapy should be assessed after 3 months of therapy and re-assessed every 3 months whilst treatment continues. The following data points must be collected by for each patient every 3 months:

- SUN cell activity score
- Total oral corticosteroid use
- Frequency of topical steroid eye drops
- Visual acuity measured by Age-appropriate LogMar assessment
- Presence of optic neuropathy,
- Presence of cataract
- Presence of hypotony
- Presence of macular oedema

Children who respond to treatment with Adalimumab (as defined by reduction of inflammation to 0.5+ cellular activity or less) will continue treatment for 18 months at which time a trial of treatment withdrawal will be undertaken. If relapse occurs, restarting Adalimumab will be considered using the same start criteria in the policy.

Serious adverse events must be reported to the MHRA using the yellow card system.

**Stop Criteria**

Adalimumab for the treatment of uveitis is stopped using following criteria:

1. 2-step increase from baseline in SUN cell activity score (AC Cells) over 2 consecutive readings
2. Sustained non-improvement with entry grade or greater for 2 consecutive readings
3. Only partial improvement (1 grade) or no improvement with the development of other ocular co-morbidity which is sustained

4. Worsening of existing ocular co-morbidity after 3 months

5. Sustained scores as recorded at entry grade measured over 2 consecutive readings (grades 1 to 2) still present after 6 months of therapy

6. Less than 0.5+ cellular activity at 18 months of treatment

8 Patient Pathway

Mild Uveitis at presentation which persists despite conventional treatment
Children with mild uveitis who have no sight threatening features (see Section 1) will be treated with topical corticosteroids by their local teams. Should active uveitis ≥ +1 cells persist beyond 3 months despite the use of topical steroid eye drops at a frequency of twice per day, referral will be made to the Specialised Ophthalmology Centre.

Severe Uveitis at presentation
Children who present with, or who develop, sight threatening features (see Section 1) will be treated with periocular corticosteroid injection, and commenced on systemic steroid treatment, by their local teams (including a paediatrician), and referred to the Specialised Ophthalmology Centre. These centres will have the input of paediatricians, paediatric rheumatologists and ophthalmologists.

Following 3 months treatment with an appropriate dose of methotrexate (or sooner in the event of methotrexate intolerance), children with persistent active uveitis ≥+1 cells, will be considered for treatment with Adalimumab by the Specialised Ophthalmology Centre.

9 Governance Arrangements
Initiation of treatment with Adalimumab should always involve a suitably trained and experienced Consultant Ophthalmologist, a Consultant Paediatric Rheumatologist and a paediatric-trained Clinical Nurse Specialist (CNS).
All children who commence treatment with Adalimumab 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 will continue to deliver Adalimumab through agreed algorithms utilising 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.

Adalimumab will be commissioned and funded by NHS England through specialist regional centres.

11 Audit Requirements

In treatment collection of data is required through the Blueteq system as required in section 7.

12 Documents which have informed this Policy

Evidence review.

Sycamore trial closed report supplied in confidence to the Clinical Panel.

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 2016 with the published Sycamore trial detail.
References


