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/a

NHS England INFORMATION READER BOX		
Directorate		
Medical	**Commissioning Operations**	Patients and Information
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

Publications Gateway Reference:	**03740**
Document Purpose	Policy
Document Name	D12/P/a Infliximab (Remicade) and Adalimumab (Humira) Anti-TNF Treatment Options for Adult Patients with Severe Refractory Uveitis
Author	Specialised Commissioning Team, NHS England
Publication Date	July 2015
Target Audience	Local Team Assistant Directors of Specialised Commissioning; Regional Team IFR Leads; Finance Leads; Local Team Pharmacists; Chairs of Clinical Reference Groups; Members of Clinical Reference Groups and registered stakeholders; Acute Trust Chief Executives; Acute Trust Medical Directors; Acute Trust Chief Pharmacists
Additional Circulation List	Regional Medical Directors; Regional Directors of Specialised Commissioning; Regional Clinical Directors of Specialised Commissioning; Regional Directors of Nursing
Description	NHS England has adopted a policy to not routinely commission this specialised treatment as described in this document.
Cross Reference	
Superseded Docs (if applicable)	
Action Required	
Timing / Deadlines (if applicable)	
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Document Status

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1 Executive Summary

Policy Statement

NHS England does not routinely commission Infliximab (Remicade) and Adalimumab (Humira) As Anti-TNF treatment options for adult patients with Severe Refractory Uveitis.

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.

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. 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 specialised and are designed to focus on specific molecules released during inflammation from cells and by doing so suppress inflammation.

Infliximab (Remicade) and Adalimumab (Humira) as Anti-TNF treatment options for adult patients with Severe Refractory Uveitis have been considered by NHS England which concluded that there was not sufficient evidence to support the routine commissioning of this treatment/procedure.

2 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.

3 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.

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

Adalimumab: Also known as Humira is an anti-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).

4 Aims and Objectives

This aims and objectives of this policy are to set out the NHS England commissioning position for Infliximab (Remicade) and Adalimumab (Humira) as Anti-TNF Treatment Options For Adult Patients with Severe Refractory Uveitis.

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5 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% remain unresponsive, estimated at around 220 new patients per annum in England.

6 Evidence Base

NHS England concluded that there was not sufficient evidence to support the routine commissioning of this treatment for the indication. In the interests of transparency the evidence base that was described by the CRG is set out in Appendix A of this policy.

7 Rationale behind the Policy Statement

The use of Adalimumab (Humira) and Infliximab (Remicade) as anti-TNF alpha treatment options for adult patients with severe refractory uveitis has been considered by NHS England who concluded that there was not sufficient evidence to support the routine commissioning of this treatment/procedure.

8 Criteria for Commissioning

NHS England does not routinely commission the use of Adalimumab (Humira) or Infliximab (Remicade) as anti-TNF alpha treatment options for adult patients with severe refractory uveitis

9 Patient Pathway

Not applicable.

10 Governance Arrangements

Not applicable.

11 Mechanism for Funding

NHS England will not routinely fund the use of Adalimumab (Humira) or Infliximab (Remicade) as anti-TNF alpha treatment options for adult patients with severe refractory uveitis.

12 Audit Requirements

Not applicable

13 Documents which have informed this Policy

Not applicable

14 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).

15 Date of Review

This policy will be reviewed in April 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

1. Gritz DC, Wong IG. Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. Ophthalmology 2004;111:491–500; discussion 500.2000;8:251–61.
2. Dobner BC, Max R, Becker MD, Heinz C, Veltrup I, Heiligenhaus A, Barisani-Asenbauer T, Mackensen F. A three-centre experience with adalimumab for the treatment of non-infectious uveitis. Br J Ophthalmol. 2013 Feb;97(2):134-8
3. Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. Br J Ophthalmol 1996;80:844–8.
4. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509–16
5. Lyon F, Gale RP, Lightman S. Recent developments in the treatment of uveitis: an update. Expert Opin Investig Drugs 2009;18:609–16.
6. Teoh SC, Hogan AC, Dick AD, Lee RW. Mycophenolate mofetil for the treatment of uveitis. Am J Ophthalmol. 2008 Nov;146(5):752-60, 760.e1-3. doi: 10.1016/j.ajo.2008.03.004. Epub 2008 May 2
7. Hogan AC, McAvoy CE, Dick AD, Lee RW. Long-term efficacy and tolerance of tacrolimus for the treatment of uveitis. Ophthalmology. 2007 May;114(5):1000-6.
8. Lee RW, Greenwood R, Taylor H, Amer R, Biester S, Heissigerova J, Forrester JV, Dick AD. A randomized trial of tacrolimus versus tacrolimus and prednisone for the maintenance of disease remission in noninfectious uveitis Ophthalmology. 2012 Jun;119(6):1223-30
9. Murphy CC, Greiner K, Plskova J, Frost NA, Forrester JV, Dick AD. Validity of using vision-related quality of life as a treatment end point in intermediate and posterior uveitis. Br J Ophthalmol. 2007 Feb;91(2):154-6. Epub 2006 Sep 14
10. Kempen JH, Daniel E, Dunn JP, Foster CS, Gangaputra S, Hanish A, Helzlsouer KJ, Jabs DA, Kaçmaz RO, Levy-Clarke GA, Liesegang TL, Newcomb CW, Nussenblatt RB, Pujari SS, Rosenbaum JT, Suhler EB, Thorne JE. Overall and cancer related mortality among patients with ocular inflammation treated with

immunosuppressive drugs: retrospective cohort study. BMJ. 2009 Jul 3;339:b2480. doi: 10.1136/bmj.b2480.

11. Howe LJ, Stamford MR, Edelsten C, et al. The efficacy of systemic corticosteroids in sight-threatening retinal vasculitis. Eye 1994;8:443–7.
12. Stanbury RM, Graham EM. Systemic corticosteroid therapy--side effects and their management. Br J Ophthalmol. 1998 Jun;82(6):704-8.
13. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids Curr Opin Ophthalmol. 2000 Dec;11(6):478-83.
14. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert Panel Recommendations for the Use of Anti-Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders. Ophthalmology. 2013 Dec 17. pii: S0161-6420(13)00893-2. doi: 10.1016/j.ophtha.2013.09.048. [Epub ahead of print]
15. Cordero-Coma M, Yilmaz T, Onal S Systematic review of anti-tumor necrosis factor-alpha therapy for treatment of immune-mediated uveitis. Ocul Immunol Inflamm. 2013;21(1):19-27. doi: 10.3109/09273948.2012.723107
16. Caspi RR Understanding autoimmune uveitis through animal models. The Friedenwald Lecture. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(3):1872-9. doi: 10.1167/iovs.10-6909. Print 2011 Mar.
17. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). Prog Retin Eye Res. 2004 Nov;23(6):617-37.
18. Murphy CC, Greiner K, Plskova J, Duncan L, Frost NA, Forrester JV, Dick AD. Cyclosporine vs tacrolimus therapy for posterior and intermediate uveitis.Arch Ophthalmol. 2005 May;123(5):634-41
19. Murphy CC, Hughes EH, Frost NA, Dick AD. Quality of life and visual function in patients with intermediate uveitis. Br J Ophthalmol. 2005 Sep;89(9):1161-5.
20. RNIB Scotland 2010 a. The cost of sight loss Scotland: 2010-2020
21. Nguyen QD, Hatef E, Kayen B, Macahilig CP, Ibrahim M, Wang J, Shaikh O, Bodaghi B (2011) A cross-sectional study of the current treatment patterns in noninfectious uveitisamong specialists in the United States. Ophthalmology. Jan;118(1):184-90. doi: 10.1016/j.ophtha.2010.03.029. Epub 2010 Aug 3.

Appendix A

NHS England considered the available clinical evidence as described by the Clinical Reference Group. NHS England concluded that there was not sufficient evidence to support the routine commissioning of this treatment for the indication. In the interests of transparency the clinical case that was put to NHS England by the Clinical Reference Group is set out below for information.

"*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 (e.g methotrexate, mycophenolate mofetil, azathioprine, cyclosporine A and tacrolimus) (Lyon et al. 2009) have been employed. 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, one of the most formative data series in this disease (Kempen et al 2009).*

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, haematological, endocrine, metabolic, fluid retention, inhibition of the immune system, changes in the electrolyte balance, weight gain, diabetes, musculoskeletal and gastrointestinal 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 .

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 and Scotland. 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 expected in 2015.
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)".