AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: Adalimumab (Humira®) for the treatment of paediatric patients with severe refractory non-infectious uveitis

July 2016

KEY FINDINGS

Report background

Uveitis is a term for inflammation within the eye which, in severe cases, can lead to blindness. Corticosteroids and immunosuppressants are the mainstay treatment for uveitis, but are not always effective and can be associated with undesirable adverse effects. Adalimumab may offer an additional treatment option in paediatric patients with severe non-infectious uveitis refractory to corticosteroid and methotrexate treatments. Although it received a licence in June 2016 for the treatment of refractory non-infectious uveitis in adults, it is not licensed for this indication in children and therefore its use is off-label. Adalimumab is available for the off-label indication for paediatric patients in NHS England through clinical commissioning. A cohort of patients has been identified based on the data from individual patient funding request (IPFR) panels in NHS Wales and, based on unmet need within the service, this medicine was considered to be suitable for assessment via the One Wales process. The treatment of adults with severe refractory non-infectious uveitis is considered in a separate Evidence Status Report (ESR).

Efficacy/Effectiveness

Results from a randomised controlled trial demonstrated significant improvements in the time to treatment failure in the adalimumab group versus placebo in patients with juvenile idiopathic arthritis-associated uveitis. Single-arm studies further support the efficacy of adalimumab for the treatment of uveitis.

Safety

No new safety signals have been observed for adalimumab for the treatment of paediatric patients with severe refractory non-infectious uveitis.

Patient factors

Adalimumab is administered every two weeks by subcutaneous injection. It may be self-administered or administered by a caregiver.

Cost effectiveness

There are no published studies on the cost effectiveness of adalimumab for the treatment of severe refractory non-infectious uveitis. Limited cost effectiveness estimates have been reported in the NHS England commissioning Policy but they are subject to uncertainty due to the assumptions made in their calculation.

Budget impact

There are estimated to be 10–15 new patients per year in Wales requiring two year treatment with adalimumab for this indication. This would result in a budget impact of between £99,760 and £149,640 in year one and between £199,520 and £299,280 in year two using the list price of adalimumab together with monitoring costs.

Impact on health and social care services

Minimal increased use of existing services.

Innovation and/or advantages

Adalimumab offers a new treatment choice for patients with refractory uveitis.

INTERIM PATHWAYS COMMISSIONING GROUP (IPCG)

RECOMMENDATION TO HEALTH BOARD CHIEF EXECUTIVES

(added after IPCG meeting)

BACKGROUND

Target group

The indication under consideration is adalimumab for the treatment of paediatric patients (aged ≥ 2 to ≤ 18 years) with severe refractory non-infectious uveitis.

Technology

Adalimumab is an inhibitor of the pro-inflammatory cytokine tumour necrosis factor (TNF) alpha[1]. TNF alpha has been demonstrated to play a pivotal role in the pathogenesis of uveitis[2].

Marketing authorisation date: Not applicable, off-label

Adalimumab for the treatment of paediatric patients with severe refractory non-infectious uveitis is off-label.

In June 2016 adalimumab received a licence for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate[1,3].

Dosing

In clinical trials, adalimumab was administered by subcutaneous injection every two weeks up to a frequency of once a week according to clinical response, at a dose of 20 mg for patients weighing < 30 kg or 40 mg for patients weighing ≥ 30 kg for up to 24 months[4,5].

Clinical background

Uveitis is inflammation primarily of the uveal tract, although inflammation of nearby tissues, including the retina and optic nerve, may also occur, with potential for significant ocular damage and blindness[6]. Uveitis is classified according to the location of inflammation and although usually bilateral, can affect one or both eyes[6]. Anterior uveitis, the most common form, is associated with inflammation of the iris. Intermediate uveitis affects the ciliary body, pars plana and anterior vitreous[6]. Posterior uveitis affects the back of the eye, including the choroid retina and optic nerve head. Panuveitis signifies inflammation of the whole uveal tract, including the anterior and posterior chambers[6].

Uveitis may be acute: sudden onset of inflammation which resolves within 3 months of treatment; recurrent: repeated episodes, separated by periods of inactivity without treatment, for more than three months, or chronic: persistent inflammation lasting more than three months in which prompt relapse (within three months) occurs when treatment is discontinued[6]. Uveitis in childhood is frequently associated with various inflammatory arthropathies, predominantly juvenile idiopathic arthritis (JIA) which is associated with approximately 20–25% of all uveitis cases[7]. However, several cases in children show no associated signs or symptoms and are thus labelled idiopathic[8]. Despite current screening guidelines and (pre-biologic) therapeutic options it is estimated that 10–15% of children develop bilateral visual impairment[5].

Incidence/prevalence

The annual 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 is 30/100,000[7]. Based on these data, in Wales with a population of approximately 560,000 children (aged 2 years up to 18)[9], the annual incidence of uveitis is 24–34 children and the prevalence is 168 children. It is estimated that 41% of JIA patients with uveitis do not respond to topical corticosteroids[10], with 30% of this group remaining unresponsive to second-line methotrexate (MTX) and are therefore potentially eligible for adalimumab treatment[11]. This equates to an incidence of 3–4 new patients per year in Wales, with a prevalent population of 21 patients. Clinical experts indicate this figure is more likely to be in the region of 10–15 new patients per year, treated for two years.

The percentage of patients failing first- and/or second-line therapies differs between paediatric and adult populations (see ESR: adalimumab for the treatment of adult patients with severe refractory non-infectious uveitis). When using the adult failure rates the estimated annual incidence of uveitis in children is 0.2–0.3 and the prevalence is 1.4 children.

Current treatment options

Initial treatment of uveitis in children is with local therapy (topical corticosteroid eye drops or peri- and intra-ocular steroid injections, depending on the severity)[7]. If initial treatment does not induce remission, local therapy may be combined with short term high dose systemic corticosteroids (either orally or intravenously). Children with severe features at presentation, or whose disease cannot be controlled with topical plus systemic corticosteroids proceed to treatment with a second-line agent, which can allow a reduction in the corticosteroid dose and their associated complications. The standard initial second line agent, for JIA is MTX. MTX 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[7].

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 medicines[7]. There is little evidence (and no randomised control trial evidence) that these medicines 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[7].

Adalimumab is licensed for the treatment of active polyarticular JIA in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs[1]. Adalimumab and infliximab have been noted to be associated with improvement in children with concomitant uveitis[7]. This has led to their use in the treatment of severe uveitis in children who do not have a diagnosis of polyarticular JIA, but have JIA-like uveitis of sufficient severity to merit their use[7]. Other biologic therapies used in the treatment of chronic anterior uveitis associated with JIA are shown in Table 1.

Table 1. Biological immunosuppressants used in the treatment of JIA-associated uveitis[12]

Target	Drug name	Dosage and route	Evidence
TNF alpha	Etanercept	Not recommended for treatment of JIA-U	RCT: no more effective than placebo. Case reports of new uveitis on etanercept
	Infliximab	6 mg/kg IV initially, then 3–10 mg/kg. Second dose at 2 weeks, then every 4–8 weeks depending on response	Several case series showing efficacy
	Adalimumab	24 mg/m^2 sc q2w. In practice often 20 mg sc q2w (body weight < 30 kg), 40 mg sc q2w (body weight ≥ 30 kg)	Several case series showing efficacy. RCTs in progress
	Golimumab	50 mg sc q2w	Case series (n = 3) showing efficacy
IL-6	Tocilizumab	10 mg/kg (body weight < 30 kg), 8 mg/kg (body weight > 30 kg) IV q4w	Case series (n = 3) and case report showing efficacy. Phase II trial in progress
CD80/86 (CTLA4)	Abatacept	10 mg/kg IV at weeks 0, 2, 4 then q4w	Case series (n = 7 and n = 2) showing efficacy. Lack of sustained response in severe uveitis (n = 21)
CD20	Rituximab	375 mg/m^2 or 750 mg/m^2 IV, two doses 2 weeks apart	Case series (n = 10 and n = 8) with long-term follow-up) showing efficacy in most patients

CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IL: interleukin; IV: intravenous; JIA-U: juvenile idiopathic arthritis-associated uveitis; q2w: every 2 weeks; q4w: every 4 weeks; RCT: randomised controlled trial; SC: subcutaneous; TNF; tumour necrosis factor

In NHS England the National Commissioning Board have published an "Interim Commissioning Policy: adalimumab for children with severe refractory uveitis" and agreed to routinely commission adalimumab for this indication on an interim basis until the details of the Sycamore trial are published. In this Policy children eligible for adalimumab have sight-threatening uveitis and have not shown an adequate response to topical steroid eye drops plus full dose MTX (or be intolerant of full dose MTX), and otherwise require prolonged high doses of systemic corticosteroids to control their disease. The Commissioning group stated that there is currently insufficient evidence to support the treatment of severe refractory uveitis in the absence of JIA with any other biologic[7]. Starting and stopping criteria were also included in this Policy (see appendix 2)[7].

Guidance and related advice

- NICE. Technology Appraisal (TA) 373. Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (2015)[13]
- NHS England. Interim Clinical Commissioning Policy: Adalimumab for children with severe refractory uveitis (2015)[7]
- NICE. Uveitis. Clinical Knowledge Summary (2014)[6]
- Scottish Uveitis Network. Treatment guidelines (2010)[14]
- British Society for Paediatric and Adolescent Rheumatology. Guidelines for screening for uveitis in juvenile idiopathic arthritis (JIA) produced jointly by BSPAR and the RCPOphth (2006)[15]

A committee of the American Uveitis Society have reviewed the use of anti tumour necrosis factor agents for the treatment of ocular inflammatory disorders the recommendations from which are provided in Appendix 1.

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) identified one randomised controlled trial investigating the clinical effectiveness, safety and cost-effectiveness of adalimumab in patients with JIA-associated uveitis. The search also identified several single-arm studies investigating the effectiveness and safety of adalimumab in paediatric patients with idiopathic or JIA-associated uveitis. The studies are briefly described below.

Efficacy

Clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE) trial

This was a randomised placebo-controlled trial designed to investigate the clinical effectiveness, safety and cost effectiveness of adalimumab in combination with MTX for the treatment of uveitis associated with JIA[5].

Patients (n = 90) aged 2 to 18 years with active JIA-associated uveitis, despite stable MTX treatment for at least 12 weeks, were randomised 2:1 to receive either adalimumab (n = 60) or placebo (n = 30)[5]. All patients received a stable dose of MTX plus either adalimumab (20 mg for patients weighing < 30 kg or 40 mg for patients weighing ≥ 30 kg) or placebo administered via subcutaneous injection every two weeks. All patients were treated up to a maximum period of 18 months, with follow up of two years from randomisation. The primary endpoint was time to treatment failure, defined by the Standardisation of the Uveitis Nomenclature (SUN) criteria[5].

The trial was stopped early for efficacy after 90 patients had been randomised as interim analysis met the pre-specified statistical stopping guidelines. The final analysis of the primary outcome showed a statistically significant increase in time to treatment failure in the adalimumab group versus placebo (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.13–0.52; $p < 0.0001$)[5]. There were a total of 16 (26.7%) treatment failures in the adalimumab group compared to 18 (60%) failures in the placebo group. The majority of treatment failures were due to missed doses and participants taking concomitant medications. Two participants from the adalimumab group and seven from the placebo group had sustained anterior chamber (AC) cell scores following six months of therapy. No significant differences were reported in quality of life scores.

Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis study

This was a retrospective observational study to evaluate the efficacy of adalimumab in JIA-uveitis[10]. JIA patients with chronic anterior uveitis (n = 20) for more than two years, non-responsive and/or non-compliant to topical therapy and second-line agents received adalimumab subcutaneously every two weeks (40 mg to 18 patients and 20 mg to two patients weighing < 30 kg). The mean duration of adalimumab therapy was 18.7 months. The majority of patients (95%) had previously failed anti-TNF alpha therapy for their uveitis (etanercept or infliximab) due to inefficacy or side-effects. The mean age of patients was 13.4 years and the mean duration of uveitis was 8.7 years[10].

The activity of uveitis was evaluated by AC inflammation according to the SUN criteria[16], where the activity of AC inflammation was graded from 0 to 4. An improved activity was defined as either a two-step decrease in the level of inflammation or a decrease to inactive (grade 0) and a worsening of inflammation as either a two-step increase in the level of inflammation or an increase to the maximum grade (4+). If one eye improved but the other worsened, the interpretation was increased activity[10]. Results showed improved activity in 35%, worsening activity in 5% and no change in the activity of uveitis in 60% of patients. The seven patients with improved activity were significantly younger (mean age 11.0 versus 14.7

years p = 0.046) and had significantly shorter disease duration (7.4 versus 11.3 years p = 0.019). Twelve patients were treated with prednisolone together with adalimumab at the start of this study. At the last follow-up seven patients had discontinued systemic prednisolone therapy[10].

Adalimumab in the therapy of uveitis in childhood

This was a retrospective study to investigate the efficacy and safety of adalimumab on juvenile uveitis, and when associated, on juvenile arthritis[17]. Children or young adults (n = 18) were included when previous therapy had been ineffective for the control of uveitis, consisting of at least one additional immunosuppressive drug in addition to corticosteroids. Seventeen of these patients had JIA and one child had no detectable underlying disorder. The age at the beginning of arthritis varied from 0.5–15 years and of uveitis from 2–19 years. Previous therapy consisted of systemic corticosteroids (n = 18), ciclosporin A (n = 18), MTX (n = 18), azathioprine (n = 12), mycophenolate mofetil (n = 4), cyclophosphamide (n = 2), leflunomide (n = 3), etanercept (n = 8) and infliximab (n = 5). Patients received adalimumab at a dose of 20–40 mg every two weeks depending on body weight. If ineffective, as was the case in one child, the treatment interval was reduced to one week; in one child treatment interval was every three weeks. On starting adalimumab the previous treatment was stopped (in children receiving other TNF alpha-blocking agents) or slowly tapered. The median observation period for children in which this strategy was effective for arthritis and uveitis (n = 13), was 16.8 months[17].

The primary outcome parameter was the recurrent rate of uveitis or arthritis[17]. A relapse of uveitis was defined as increase of the cells in the AC of 2+ or more (or from 3+ to 4+), according to the SUN criteria. Baseline for a changing recurrence frequency was an observation period of at least 2 years before initiation of adalimumab and at least 6 months after beginning of treatments. The grading for uveitis was: effective: no relapse or more than two relapses less than before treatment; mild: one relapse less than before treatment; no response: no change in relapse rate; worsening: more relapses under treatment than before[17]. The effect of adalimumab on arthritis will not be discussed in this report.

Results showed that adalimumab was effective in 16 children, mildly effective in one and one child did not demonstrate any beneficial effect[17]. Median response was six weeks (range 2-16 weeks). Additional immunosuppressive treatment was used in seven of the effectively treated patients. In 15 children systemic corticosteroids were stopped and in the remaining three children a reduction to a lower dose was possible[17].

Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis

This was a retrospective study to investigate the long-term effects of adalimumab in the treatment of uveitis associated with JIA[4]. Adalimumab was initiated in 54 patients with JIA and uveitis non-responsive or intolerant to standard immunosuppressive therapy. Adalimumab was administered at a dose of 24 mg/m^2 at 14-day intervals subcutaneously, and according to clinical response, up to a frequency of 24 mg/m^2 at seven-day intervals for a mean of two years. Adalimumab was the first anti-TNF treatment for 22 patients. Twenty nine patients had previously not responded to anti-TNF agents (etanercept or infliximab). The median age at the end of the study was 15 years.

Evaluation of the efficacy of adalimumab on uveitis activity was performed using the SUN criteria[16] and clinical examination. The clinical response to treatment for uveitis was considered good if there were < 3 AC cells/1 mm slit and there was no need for corticosteroid drops; moderate if there were 3–9 AC cells/1 mm slit and there was no need for more than three corticosteroid drops per day; ineffective if there were > 10 AC cells and more than three corticosteroid drops required per day.

At the end of the study, results showed good clinical control of uveitis in two thirds of patients; 31% not needing any local treatment and 35% only requiring 1-2 corticosteroid

drops per day. One third of patients still had active uveitis and used ≥ 3 corticosteroid drops per day. According to the SUN criteria[16], the response to adalimumab treatment was improved in 28% of patients and worsened in 13% of patients. Together with the 30% of patients whose response to adalimumab was moderate, an overall positive effect of adalimumab was observed in 57% of patients with uveitis. Adalimumab therapy was stopped in five patients after a short period due to adverse events or inefficacy.

Systemic corticosteroid therapy could be stopped in 22% of patients. At the end of the study, only four patients remained on adalimumab monotherapy, and the remainder were on combination therapy with corticosteroids and/or immunosuppressants. Twenty five patients were receiving adalimumab every fortnight and 24 patients were receiving it weekly. The main clinical reason for weekly treatment was activity of uveitis[4].

Safety

The Summary of Product Characteristics (SPC) lists adverse events (AEs) that may be associated with adalimumab treatment[1]. These AEs include, but are not limited to, infections (such as nasopharyngitis, upper respiratory tract infection, sinusitis and tuberculosis), hypertension, injection site reactions, gastrointestinal disorders, headaches, musculoskeletal pain and haematological reactions[1]. Patients taking anti-TNF agents are more susceptible to serious infections (e.g. tuberculosis) and are therefore closely monitored for such infections during and after treatment with adalimumab[18]. The SPC also states that TNF-antagonists including Humira® have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. An association between demyelinating disorders and in particular intermediate uveitis has been described in the scientific literature. Ophthalmologists are advised to consult specialists experienced in the use of Humira® before initiation of such treatment. Prescribers are furthermore advised to consider discontinuation of Humira® if any of these disorders develop[1]. Serious AEs occurred in 21.7% of patients treated with adalimumab versus 6.7% of patients treated with placebo in the SYCAMORE trial. Infections and infestations were the most commonly reported serious AEs in the adalimumab group. Overall, no new safety issues were identified for the treatment of severe refractory non-infectious uveitis[4,5,10,17].

The US Food and Drug Administration (FDA) have issued an alert to healthcare professionals of an increased risk of malignancies in children and adolescents treated with anti-TNF agents[19]. The data were derived mainly from children and adolescents on etanercept and infliximab therapy; data on adalimumab are scarce because of limited follow-up. Malignancy rates were not provided for untreated JIA or JIA treated with methotrexate alone. A presentation by the Royal College of Rheumatology (ACR)/ Associate Rheumatology Health professional 2009 Annual Scientific meeting reported no increased risk of anti-TNF therapy in patients with JIA[18]. A retrospective study evaluated overall and cancer mortality in relation to immunosuppressive drug exposure, including anti-TNF drugs, among adult patients with ocular inflammatory diseases[20]. The study showed an increased overall and cancer mortality in patients exposed to TNF inhibitors. However, the authors acknowledge that these data need to be interpreted with caution due to the retrospective nature of the study, limited duration of follow-up and number of patients and the prevalence of comorbidity in patients taking anti-TNF agents[20]. A systematic review and meta-analysis from 2011 based on data from patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis (age not specified) concluded that TNF treatments do not increase the risk of malignancy, particularly lymphoma. However, they do appear to increase the risk of skin cancer, including melanoma[21].

Clinical effectiveness issues

The SPC states that Humira® treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Humira® is indicated[1]. Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Humira®. Patients treated with Humira® should be given the special alert card[1].

At the time of writing, there is limited clinical evidence available in support of the use of adalimumab for the treatment of severe refractory non-infectious uveitis. The majority of such studies have investigated JIA-associated uveitis, which is unsurprising since they are frequently associated. The efficacy of adalimumab in patients with idiopathic disease is uncertain.

The SYCAMORE trial has now demonstrated benefit in relation to uveitis activity and related complications from the use of adalimumab. The NHS England Clinical Commissioning Policy indicates that infliximab has not been evaluated in the same way as adalimumab and there are no comparative trials between the two medicines, although observational studies find little difference in efficacy and it is the standard of care for treatment. In one study identified by AWTTC, adalimumab was demonstrated to be significantly superior to infliximab[22]. However several of the studies discussed in this ESR included patients who were deemed to be intolerant or had no response to prior infliximab therapy[4,10,17].

The SYCAMORE trial was the only randomised controlled study identified by AWTTC. The results from this trial suggest that adalimumab significantly improves the time to treatment failure versus placebo in JIA-associated uveitis non-responsive to second-line MTX therapy[5]. However, it is important to note that this study was presented as a conference abstract and full results have not yet been published. In particular, the median time to treatment failure, cost-effectiveness data and the baseline characteristics (e.g. uveitis subtype and disease duration) of each group were not reported.

The remaining studies discussed in this report were small, open-label and single-arm, thus without a placebo or comparison group. Additionally, the patient baseline characteristics, the previous treatments (including TNF alpha inhibitors) received by the patients and the concomitant treatment administered with adalimumab differed within each study[4,10,17]. Some of these retrospective studies included adult patients (aged > 18 years); the results from such patients were analysed together with paediatric patients and not divided into subgroups[10,17].

The small number of patients included in one study (adalimumab in the therapy of uveitis in childhood) is likely to have favoured the response rate which reported an improvement of ocular inflammation in 89% of patients following adalimumab therapy[17]; such results are far superior to the response rates reported from the other studies.

The long-term retrospective study, one of the largest cohort studies, reported an improvement in 66% of patients with JIA-associated uveitis based on clinical examination and an improvement in 57% of patients according to SUN criteria[4]. The authors claim that the SUN criteria is difficult to use for the evaluation of JIA-associated uveitis, since the number of AC cells is often quite small when the eye disease is active, consequently making a two-fold difference difficult to achieve; and that clinical examination by an experienced ophthalmologist may be better. Five patients discontinued adalimumab therapy due to adverse events or inefficacy. However, the nature of the adverse events experienced by these patients was not reported

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

Reviews of the literature did not locate any robust published cost-effectiveness evidence. However, the NHS England Clinical Commissioning Policy has evaluated the use of adalimumab for paediatric patients with severe refractory uveitis. The appendix of the Policy includes limited information relating to the cost-effectiveness of anti-TNF alpha treatment in ocular inflammatory disease, including uveitis.

The NHS England Policy suggests that NICE guidance on the treatments of age-related macular degeneration (AMD), retina vein occlusion, and diabetic retinopathy are valuable in terms of the visual outcomes associated with uveitis; thereby providing rationale for use of data from these patients groups to guide model assumptions and inputs. It further highlights how some forms of uveitis result in complete blindness, enucleation, disfigurement and discomfort. Whilst other forms are associated with a high risk of requirement for surgery, which itself can increase the risk of blindness. Cost of surgery for this patient group is estimated at around £2,000 per patient[7].

The NHS England Policy also suggests that the costs associated with blindness are notably different for monocular and bilateral vision loss. Those with childhood onset monocular visual loss are at a considerably greater lifetime risk of bilateral loss compared to the elderly. Unilateral costs are estimated to amount to 4% of the lifetime costs of bilateral blindness. However, there is no rationale provided for this approach. Risk of blinding increases with age; associated costs are closely related to effects on quality of life, in addition to wider societal impacts including special educational and social services needs.

The Policy document reports utility values for different levels of vision: baseline 0.97, mid visual loss or severe unilateral vision loss 0.76, moderate visual loss 0.63, severe visual loss 0.53. The document thereby associates the loss of vision from normal (0.97) to < 6/60 (0.53) with a quality of life decrement of 0.44. However it is unclear how these data were derived.

The NHS England Policy estimates a life expectancy of 75 years for paediatric patients with uveitis, and that the cost of blindness per year (for AMD) is likely to be ≤ £6,500. If children are assumed to have a life expectancy of 75 years after visual loss, the cost of blindness in this population is estimated to be £487,500. Again, there is limited evidence to justify this estimate, but it does provide some background into the resource savings that could be achieved if blindness could be avoided, and a better appreciation of the NHS modelling approach.

The Policy document has used a variety of blindness rate data[7,23-25] together with estimates of good and poor prognosis to calculate the likelihood of: remission, persistent activity, cataract development, and cataract development resulting in blindness[7]. The estimated blindness rates appear to be based on data sourced from paediatrics; however the rates referred to in the literature are subject to a high degree of variability. This may be due to differences at baseline with regards to visual acuity (ranging from 20/20 to worse than 20/200) complications such as cataract and glaucoma, diagnosis of JIA-associated uveitis or idiopathic uveitis as well as previous and current treatments. Additionally the duration of follow-up varied between studies[23-25].

The NHS model assumes that the probability of blindness following anti-TNF treatment is 1%. This has been calculated using a treatment effect range of 60–95%. Treatment effect was evaluated by AC inflammation according to SUN criteria, which is in line with the outcomes measured in the clinical studies described in this ESR[26,27]. It is also estimated that continuation of conventional treatment is associated with a probability of blindness of 15%[7]. The assumed risk of blindness associated with immunosuppressant therapy is not fully explained.

The economic model explores five treatment strategies:

1. continue conventional treatment (MTX) – risk of blindness is 15%

2. add a conventional immunosuppressant at a cost of £15,000 for five years – risk of blindness 8%
3. add a biologic at a cost of £45,000 over five years – risk of blindness 1%
4. add a biologic at a cost of £90,000 over ten years – risk of blindness 1%
5. add a biologic at a cost of £45,000 – risk of blindness 8%

The cost utility analyses revealed that strategies 2 and 3 dominated (i.e. were less costly and more effective). However, strategy 3 was considered more desirable, as it met the assumption that a 1% risk of blindness was the upper limit of acceptance. When strategies 2 and 3 were compared (i.e. strategy 2 became the effective comparator) this produced an Incremental Cost Effectiveness Ratio (ICER) of £6,400 per quality-adjusted life-year (QALY) gained. Univariate analysis identified how the model was most sensitive to the cost of biologic treatment and risk of blindness on a biologic. When the number of years on a biologic treatment was increased to 9 years the ICER increased to £22,000 per QALY gained. When the risk of blindness on biologic was changed to 5% this significantly increased the ICER to £40,200. While this analysis provides estimates of the cost effectiveness of adalimumab, it must be treated with caution. As noted above, the sources for the data inputs are subject to a considerable amount of uncertainty, given that their sources are not entirely traceable and that some of the data relates to adults and not specifically to children. A number of assumptions have also been applied without full explanation or justification.

BUDGET IMPACT

In clinical trials, the dose of adalimumab for the treatment of severe non-infectious uveitis was 20 mg for children weighing < 30 kg and 40 mg for children ≥ 30 kg every other week.

The British National Formulary (BNF) lists the price of adalimumab (40 mg prefilled pen or syringe or 40 mg/0.8 mL vial) as £352.14[28]. Table 1 details the prediction for the budget impact in Wales. This excludes VAT and any local contracting agreements.

Table 1. Projected Budget Impact in Wales

	Year 1	Year 2	Data Source
Adalimumab (20 mg or 40 mg every other week) cost per patient per annum	£9,156*	£9,156*	BNF May 2016[28]
Number of patients treated per annum	10–15	20–30	Clinical experts
Budget impact – net medicine cost	**£91,560-£137,340**	**£183,120-£274,680**	
Monitoring costs per annum per patient	£820	£820	PSSRU 2015
Net monitoring costs per annum	£8,200-£12,300	£16,400-£24,600	
Net total budget impact	**£99,760-£149,640**	**£199,520-£299,280**	
***Assuming wastage for patients weighing < 30 kg, thus requiring the 20 mg dose.			

Budget impact issues

- Since adalimumab is for the treatment of patients with refractory disease, it was assumed that no medicines are displaced. Additionally, the costs saved from discontinuing corticosteroid therapy were not included as it is considered to be negligible to the budget impact.

- Adalimumab is assumed to be administered on alternate weeks. It is noted that in one of the studies included in the efficacy section, half of patients received adalimumab once weekly.

- The budget impact has assumed 100% success rate and has not considered the discontinuation and mortality rate. Clinical experts have highlighted that relapse is very common (up to 80%).

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Adalimumab is not licensed to treat this indication and is therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

APPENDICES

Appendix 1

A US expert panel, rather than an evidence-based review, have provided recommendations for the use of anti-TNF alpha biologic agents in patients with ocular inflammatory disorders[29]. Substantial evidence was identified from 400 publications over 15 years, supporting the use of anti-TNF therapies for several well-recognised forms of uveitis:

1. Strong recommendation. Infliximab (good-quality evidence) or adalimumab (moderate-quality evidence) should be considered early in management of patients with vision-threatening ocular manifestations of Behçet's disease.
2. Strong recommendation. Infliximab (good-quality evidence) or adalimumab (good-quality evidence) should be considered as second-line immunomodulatory therapy for children with vision-threatening uveitis secondary to JIA in whom methotrexate therapy is insufficiently effective or not tolerated. Methotrexate therapy, if tolerated, may be combined with infliximab therapy.
3. Strong recommendation. Infliximab or potentially adalimumab should be considered as second-line immunomodulatory therapy in patients with vision-threatening chronic uveitis from seronegative spondyloarthropathy (good- to moderate-quality evidence).
4. Discretionary recommendation. Infliximab or adalimumab for other forms of ocular inflammation, including sarcoidosis, scleritis and panuveitis, may be considered in patients with vision-threatening, corticosteroid-dependent disease who have failed first-line immunomodulatory therapies such as antimetabolites or calcineurin inhibitors (moderate-quality evidence). The literature for adalimumab is less developed than for infliximab, but these agents seem to show similar efficacy in most studies. Until more comparative data are available, no recommendation can be made as to preferred agent, although numerous studies have suggested that adalimumab may be effective in patients who have become intolerant to or have developed reduced clinical responsiveness to infliximab.
5. Strong recommendation. Use of infliximab or adalimumab should be considered before etanercept therapy for treatment of ocular inflammatory disease. Etanercept may have efficacy for treatment of some forms of ocular inflammatory disease such as mucocutaneous Behçet's disease, but it has been associated with development of uveitis in JIA patients and development of sarcoid-like disease in others. Patients presently taking etanercept for other indications with existing, incompletely controlled uveitis or new ocular inflammatory disease should consider switching to infliximab or adalimumab if possible[29].

Appendix 2
Start criteria from the NHS England commissioning Policy[7]:

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 of less with:
   - 0.1 mg/kg/day of oral prednisolone in combination with MTX (minimum dose of 10 mg/m^2 with a maximum dose of 25 mg/m^2) and 2 drops of topical steroid eye drops per day
   - Treatment effect should be assessed after at least 12 weeks
   - When the patients is MTX intolerant an adequate trial (3–6 months) of an alternative conventional immunosuppressant should be given
   - Exceptionally a child presenting with severe sight threatening disease will be considered for adalimumab before the end of a 12 week trial of prednisolone and MTX.
   -

Very severe sight threatening features at presentation include:
- Severe inflammatory activity (≥ 3+ cells)
- Cataract
- Glaucoma (intraocular pressure > 21 mmHg with evidence of optic neuropathy)
- Hypotony (intraocular pressure ≤ 5mmHg)
- Dense vitreous opacity
- Macular oedema causing visual impairment ≤ 6/18.

Stop criteria from the NHS England commissioning Policy:

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[7].

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