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

Adalimumab for the treatment of paediatric patients with severe refractory non-infectious intermediate, posterior and pan- uveitis

January 2019

ONE WALES INTERIM COMMISSIONING DECISION

Adalimumab for the treatment of paediatric patients with severe refractory non-infectious intermediate, posterior and pan- uveitis

Date of original advice: October 2016
Date of review: January 2019

The following Interim Pathways Commissioning Group (IPCG) recommendation has been endorsed by health board Chief Executives.

Using the agreed starting and stopping criteria adalimumab can continue to be made available within NHS Wales to treat paediatric patients (aged ≥ 2 to ≤ 18 years) with severe refractory non-infectious intermediate, posterior and pan- uveitis.

Adalimumab should be initiated in specialist centres for this indication.

Adalimumab is not licensed to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before this medicine is prescribed.

The risks and benefits of the off-label use of adalimumab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Interim Commissioning decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Interim Commissioning decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for adalimumab for the treatment of paediatric patients with severe refractory non-infectious intermediate, posterior and pan- uveitis

These criteria are taken from the NHS England Clinical Commissioning policy document[1] with further adaptation from clinical experts, University Hospitals Bristol NHS Foundation and Translation Health Science (Ophthalmology), Bristol Medical School, Faculty of Health Sciences.

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, and/or vitritis and/or clinically active chorioretinal lesions and/or macular oedema, defined as a sustained grade of ≥+1 cellular infiltrate in the anterior chamber, BIO score of >/= 1 and OCT evidence of macular oedema
AND
2. Failure to control uveitis to +0.5 cells or BIO score or persistent macular oedema or less with:

- Methotrexate (minimum dose of 10 mg/m^2 with a maximum dose of 25 mg/m^2) or mycophenolate mofetil, usually in combination with
- 0.1mg/kg/day of oral prednisolone
  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 or mycophenolate mofetil.

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 – BIO score of >/+ 2
- Macular oedema causing visual impairment ≤6/18 or >/= to CMT of 350um

As this is an unlicensed treatment clinicians must follow their employers' requirements regarding patient/carer consent for treatment.

Adalimumab should always be initiated in a specialised ophthalmology centre.

The dose of adalimumab administered in clinical trials was 20 mg for patients weighing < 30 kg and 40 mg in patients weighing ≥ 30 kg every 2 weeks.

Dose frequency may be escalated to 40 mg once every week if safe to do so in patients with partial response and sight-threatening disease within three months of treatment. If no response is achieved in three months then treatment is considered a failure and treatment should be stopped.

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:

- Standardisation of the Uveitis Nomenclature (SUN) cell activity score
- Total oral corticosteroid use
- Frequency of topical steroid eye drops
- Visual acuity measured by age-appropriate Logarithm of Minimum Angle of Resolution (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 or BIO score of 0.,5 or less or resolution of macular odema) 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 the following criteria:
1. 2-step increase from baseline in SUN cell activity score (anterior chamber [AC] cells) or BIO score or maintained macular oedema over 2 consecutive readings at least a month a part
2. Sustained non-improvement with entry grade or greater for 2 consecutive readings
3. Worsening of existing ocular co-morbidity after 3 months if deemed due to persistent inflammation and not a result of progressive structural damage due to previous inflammation
4. Sustained scores as recorded at entry grade measured over 2 consecutive readings (grades 1 to 2) still present after 6 months of therapy
5. Less than 0.5+ of cellular activity or BIO score or resolution of macular oedema at 18 months of treatment

Refer also to the dosing section above under “starting criteria”.

Reference

NHS England. Interim Clinical Commissioning Policy: Adalimumab for children with severe refractory uveitis. Ref. D12X02. 2015. Available at: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/11/d12x02-paediatric-uveitis-anti-tnf.pdf Accessed Jun 2016.

This is a summary of new evidence available and patient outcome data collected, to inform the review.

Background

Uveitis is a term for inflammation within the eye which, in severe cases, can lead to blindness. Uveitis is classified according to the location of inflammation: anterior, intermediate, posterior and pan- uveitis. Adalimumab was licensed in 2017 for use in children from two years of age for the treatment of chronic, non-infectious anterior uveitis who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate[1]. Adalimumab is recommended for use in this indication by the All Wales Medicines Strategy Group (AWMSG)[2]. Treatment of non-anterior uveitis remains off-label and is currently supported by One Wales Interim Commissioning advice. Adalimumab is available in NHS England under the commissioning medicines for children in specialised services policy in line with the National Institute for Health and Care Excellence technology appraisal guidance for adults[3,4].

Current One Wales Interim Commissioning Decision

Using the agreed starting and stopping criteria, adalimumab (Humira®) can continue to be made available within NHS Wales to treat paediatric patients (aged ≥ 2 to ≤ 18 years) with severe refractory non-infectious uveitis. Reviewed November 2017[5].

Licence status

Adalimumab (Humira®) for the treatment of severe refractory non-infectious intermediate, posterior and panuveitis remains an off-label indication.

Guidelines

- Constantin T, Foeldvari I, Anton J et al (2018). Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative[6]
- Dick AD, Rosenbaum JT, Al-Dhibi HA et al (2018). Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative[7]

Both of the above guidelines recommend use of adalimumab for refractory uveitis[6,7]. The SHARE initiative recommends the use of anti-tumour necrosis factor strategies (adalimumab> infliximab> golimumab) in line with the starting and stopping criteria quoted in the One Wales Interim Commissioning advice[5,6].

AWMSG recommended the use of adalimumab (Humira®) for the treatment of paediatric chronic non-infectious anterior uveitis in patients from two years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate. December 2017[2].

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines

There remain no alternative medicines licensed for this stage of the disease.

Efficacy/Effectiveness

A repeat literature search conducted by AWTTC (4 October 2018) identified two retrospective studies since the previous review evaluating the efficacy of adalimumab for the treatment of non-anterior uveitis in paediatric patients[8,9]. One study did not report results by ocular site of uveitis and therefore will not be discussed further[8]. The second study was a case series of 12 patients, median age 13 years: six patients had pan-uveitis; one patient had intermediate uveitis; and five patients had anterior uveitis[9]. Patients with anterior uveitis received topical corticosteroids and those with intermediate or pan- uveitis received systemic corticosteroids as first-line treatment. Ten patients were started on adalimumab in combination with methotrexate. Overall adalimumab was able to control ocular inflammation during a median of 36.5 months (interquartile range 23–46 months). None of the patients who received adalimumab reported serious or life-threatening adverse effects. One patient with psoriatic arthritis developed new onset severe palmoplantar psoriasis which improved after discontinuation of therapy[9].

The seven patients with non-anterior uveitis ranged from 11 to 18 years old, five had bilateral and two had unilateral uveitis (n = 12 eyes in total)[9]. Treatment with adalimumab ranged from 24 to 67 months and was intensified in two patients. The median best corrected visual acuity (BCVA) for

all 12 eyes was +0.5 lines, BCVA improved in 6 of 12 eyes (median = +4.5 lines), was maintained in 5 of 12 (0 lines) eyes and decreased in 1 eye (−1 line)[9].

Safety
No new significant safety issues were identified.

Cost effectiveness
A cost-utility analysis which compares adalimumab in combination with methotrexate versus methotrexate alone, for the management of uveitis associated with juvenile idiopathic arthritis has recently been published[10]. Utilities and resource data used in the model were informed by the SYCAMORE study. However, the eligibility criteria for SYCAMORE included patients with anterior uveitis and may be less relevant to the patient population being considered here. Clinical expert opinion indicates that non-anterior uveitis is more severe and associated with worse outcomes compared with anterior uveitis. Transitional probabilities were taken from a 10-year longitudinal cohort study of paediatric patients with uveitis. Of the 157 patients included in this cohort, 37 had non-anterior uveitis. The base case indicated that adalimumab in combination with methotrexate resulted in additional costs of £39,316 with a 0.30 quality-adjusted life-year (QALY) gain compared with methotrexate alone, resulting in an incremental cost-effectiveness ratio of £129,025 per QALY gained. In a scenario where patients in the methotrexate alone group were visually impaired for the duration of the model and patients in the adalimumab group had no visual impairment, the ICER reduced to £53,072 per QALY gained[10].No sub-group analyses were performed on the non-anterior uveitis group.

Budget impact
[Confidential data removed]. Three biosimilar adalimumab preparations are now available[11-13]. The list price for these biosimilars is 8–10% lower than the cost of the reference medicine, Humira®[14]. This however does not take in to account any future contract prices which may be significantly different to the list prices for the reference product and the biosimilars.

Impact on health and social care services
No new information has been provided.

Patient outcome data
[Confidential data removed].

Next review date: January 2020

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