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

July 2020

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: July 2020

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 (i.e. intermediate, posterior and pan-uveitis) remains off-label and is currently supported by One Wales 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[3-5].

Current One Wales Decision
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. Reviewed January 2019[6].

Licence status
Adalimumab for the treatment of severe refractory non-infectious intermediate, posterior and pan-uveitis remains an off-label indication.

Guidelines
There are no changes to current guidelines.

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines
There remain no alternative medicines licensed for non-anterior uveitis in paediatric patients.

Efficacy/Effectiveness
A repeat literature search identified two additional studies evaluating adalimumab for the treatment of uveitis in paediatric patients[7,8]. The first study was a retrospective, chart review over an eight year period that provided real-world data on the use of biological therapies for the treatment of uveitis in paediatric patients from Sydney, Australia[7]. Of the 27 patients included in the study, 23 had anterior uveitis, 1 had intermediate uveitis and 3 had posterior or panuveitis. The most common aetiological diagnosis was juvenile idiopathic arthritis-associated uveitis (n = 18) followed by idiopathic uveitis (n = 8), and one case of Blau syndrome. The majority of patients received adalimumab (n = 23); three patients received infliximab and one patient received anakinra. Treatment by ocular site was not reported. The mean follow-up was 23.4 months (range 0-67 months). Results showed an improvement in intraocular inflammation with maintained visual acuity in patients with non-anterior uveitis[7].

The second study was a retrospective review of five male, Chinese, paediatric and adolescent patients who received adalimumab for the treatment of Behcet's disease-related uveitis[8]. One patient with panuveitis was an adult (aged 20 at uveitis onset). Of the paediatric patients, two had panuveitis, one had posterior uveitis and one had intermediate uveitis. The duration of adalimumab treatment in the paediatric population ranged from 24 to 41 months. The adult patient received adalimumab for seven months. In all patients, best corrected visual acuity statistically significantly improved at 12 months compared with baseline. In paediatric patients (n = 4), results showed complete resolution of inflammation in all eyes (n = 8), retinal vasculitis resolved in all cases and corticosteroid dose was reduced at 6 months of treatment[8].

Safety
In the first study, adverse events related to biological therapy were reported in five patients (18.5%): anaphylaxis, preseptal cellulitis, facial rash, lymphadenopathy and viral respiratory infection[7]. The specific biological therapy associated with these adverse events was not reported[7]. In the second study no patients developed any adverse events associated with adalimumab treatment[8].

Cost effectiveness
There are no new cost-effectiveness data.

Budget impact
[Confidential data removed]. This figure is in line with the estimated number of patients considered to be eligible for treatment per year by clinical experts.

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

Patient outcome data
[Confidential data removed].

References

1. European Medicines Agency. Humira®. Procedural steps taken and scientific information after the authorisation. Aug 2019. Available at: https://www.ema.europa.eu/en/documents/procedural-steps-after/humira-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Accessed Nov 2019.
2. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2717. Adalimumab (Humira®) 40 mg solution for injection. Dec 2017. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/3035. Accessed Nov 2019.
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6. All Wales Therapeutics and Toxicology Centre. One Wales Interim Commissioning Decision: Adalimumab for the treatment of paediatric patients with severe refractory non-infectious intermediate, posterior and pan-uveitis. Jan 2019. Available at: https://www.awttc.org/pams/current-one-wales-interim-commissioning-decisions. Accessed Nov 2019.
7. Oh L, Nguyen C, Phan K et al. Changing biological disease modifying treatment for paediatric uveitis in the real world. *Clinical and Experimental Ophthalmology.* 2019;47:741-748.
8. Ho M, Chen L, Sin H et al. Experience of using adalimumab in treating sight-threatening paediatric or adolsecent Behcet's disease-related uveitis. *Journal of Ophthalmic Inflammation and Infection.* 2019;9(14).