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

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

November 2017

ONE WALES INTERIM COMMISSIONING DECISION PARTIALLY SUPERSEDED BY AWMSG ADVICE ISSUED DECEMBER 2017 (REFERENCE NUMBER 3035)

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ONE WALES INTERIM COMMISSIONING DECISION

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

Date of original advice: October 2016
Date of review: November 2017

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

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.

Adalimumab (Humira®) should be initiated in specialist centres for this indication.

Adalimumab is licensed for the treatment of anterior uveitis but not for other forms of uveitis in paediatric patients. As such, the latter indication remains 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 the treatment of severe refractory non-infectious intermediate uveitis, posterior uveitis and panuveitis 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 uveitis

These criteria are taken from the NHS England Clinical Commissioning policy document[1].

Starting and stopping criteria

Starting criteria:

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

A) The presence of active anterior uveitis, defined as a sustained grade of ≥ +1 cellular infiltrate in the anterior chamber
AND
Failure to control uveitis to +0.5 cells or less with:

- methotrexate (minimum dose of 10 mg/m^2 with a maximum dose of 25 mg/m^2), usually in combination with
- 0.1 mg/kg/day of oral prednisolone
  and
- 2 drops of topical steroid eye drops per day.

OR

B) The presence of active posterior segment uveitis defined as binocular indirect ophthalmoscopy (BIO) score ≥ 1 or cystoid macular oedema or sight-threatening retinal, retinal vascular or choroidal inflammation
AND
Failure to control uveitis with:

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

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 > 21 mmHg with evidence of optic neuropathy)

- hypotony (Intraocular pressure ≤ 5 mmHg)
- dense vitreous opacity
- macular oedema causing visual impairment ≤ 6/18.

As adalimumab is unlicensed for the treatment of severe refractory non-infectious intermediate, posterior and panuveitis, clinicians must follow their employers' requirements regarding patient/carer consent for treatment of this indication.

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 for each patient every 3 months:

- Standardisation of the Uveitis Nomenclature (SUN) cell activity score
- BIO 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 and BIO score 0.5 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.

Stopping 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 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 and BIO score 0.5 at 18 months of treatment

Refer also to the dosing section above under "starting criteria".

Reference

1 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 panuveitis. Adalimumab was licensed in 2016 for use in adults with refractory non-infectious intermediate, posterior and panuveitis, and is recommended for use in this indication (with some restrictions) by the National Institute for Health and Care Excellence. At the time of the One Wales Interim Commissioning decision, adalimumab for the treatment of children with uveitis was off-label. Adalimumab is available in NHS England through clinical commissioning for the treatment of severe refractory uveitis in children[1].

A cohort of patients were identified through data from individual patient funding requests (IPFR) panels in NHS Wales and based on unmet need within the service, this medicine was considered suitable for assessment via the One Wales process.

Current One Wales Interim Commissioning Decision

Using the agreed starting and stopping criteria, adalimumab (Humira®) can be made available within NHS Wales to treat paediatric patients (aged ≥ 2 to ≤ 18 years) with severe refractory non-infectious uveitis. October 2016.

Licence status

On 5 September 2017, adalimumab (Humira®) received a licence extension, granted by the European Medicines Agency, for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate[2].

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

Guidelines

The All Wales Medicines Strategy Group (AWMSG) is currently appraising adalimumab for the treatment of non-infectious anterior uveitis in children. An AWMSG recommendation to Welsh Government will be made in December 2017 and advice should be published shortly after.

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines

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

Efficacy/Effectiveness

The SYCAMORE study has now been published in a peer reviewed journal and was the pivotal study cited in the European Medicines Agency assessment report for the license extension[3,4]. This study, initially available as a conference abstract, was considered to inform the original One Wales Interim Commissioning recommendation. The data reported in the published paper are consistent with those reported in the evidence status report (ESR)[3]. The Committee for Medicinal Products for Human Use (CHMP) did not consider that the evidence was sufficient to support extrapolation to treatment of non-anterior uveitides. It was therefore acknowledged that with this restriction there remains a clear unmet need in paediatric patients with non-anterior (intermediate, posterior and pan-) uveitis[4].

A repeat literature search identified a German retrospective review evaluating the discontinuation of adalimumab treatment in patients (n = 68) with chronic refractory anterior uveitis associated with juvenile idiopathic arthritis[5]. Adalimumab treatment was effective and uveitis inactivity was achieved in 59 patients (86.8%) within six months of treatment. At the time of data analysis, 39 of the 59 patients were still receiving adalimumab treatment, with a mean treatment duration of 38.3 months (range 12–91 months). In 20 patients, adalimumab treatment had been discontinued after a mean of 30.6 months (range 10-65 months) due to: a loss of treatment response (n = 12); complete uveitis and arthritis inactivity for at least two years (n = 3); adverse events (n = 4) including lupus-like syndrome, alopecia, non-malignant lymph-node hyperplasia and a combination of diverse side effects (distress, dizziness, vomiting and headache); medicine cost reimbursement issues (n = 1)[5].

Safety

No new significant safety issues were identified.

Cost effectiveness
A repeat literature search found no additional cost-effectiveness evidence.

Budget impact
The number of paediatric patients receiving treatment with adalimumab over the last year has been significantly lower than the projected figures included in the original ESR by a magnitude of almost 90%. Based on patient numbers over the last year, clinical experts indicate that there are likely to be no more than two paediatric patients per year requiring treatment for non-anterior uveitides.

Impact on health and social care services
The impact on service remains minimal.

Patient outcome data
[Confidential data removed.]

Next review date: October 2018

References

1. Specialised Commissioning Team NHS England. Interim clinical commissioning policy: adalimumab for children with severe refractory uveitis. Reference: D12X02. November 2015. Available at: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/11/d12x02-paediatric-uveitis-anti-tnf.pdf. Accessed May 2016.
2. AbbVie Limited. Humira®. Summary of Product Characteristics. September 2017. Available at: https://www.medicines.org.uk/emc/medicine/31860. Accessed September 2017.
3. Ramanan A, Dick A, Jones A et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *The New England Journal of Medicine.* 2017;376(17):1637-1646. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1614160. Accessed September 2017.
4. European Medicines Agency. Assessment Report: Humira®. Procedure No.: EMEA/H/C/000481/II/0163. Jul 2017. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/human_med_000822.jsp&mid=WC0b01ac058001d124. Accessed Oct 2017.
5. Breitbach M, Tappeiner C, Bohm MR et al. Discontinuation of long-term adalimumab treatment in patients with juvenile idiopathic arthritis-associated uveitis. *Graefe's Archive for Clinical and Experimental Opthalmology.* 2017;255(1):171-177. Available at: https://link.springer.com/article/10.1007/s00417-016-3497-5. Accessed October 2017.