# Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]

Multiple Technology Appraisal

2nd meeting: 12th April 2017

Committee C

**Slides for Committee, projector and public [NoACIC]**

NICE National Institute for Health and Care Excellence

# The technologies

| Dexamethasone intravitreal implant | Adalimumab subcutaneous injection |
|---|---|
| • Ozurdex (Allergan) 0.7 mg intravitreal implant (biodegradable) in an applicator<br>• Corticosteroid that inhibits pro-inflammatory mediators<br>• £870.00 per implant (BNF Dec 2016)<br>• 6 monthly cost: £870 (source: AR) | • Humira (Abbvie) 40mg/0.4ml solution for injection every other week<br>• Monoclonal antibody that inhibits the pro-inflammatory cytokine, tumour necrosis factor (TNF)-alpha<br>• £704.28 per two prefilled pens/syringes or vials (BNF Dec 2016)<br>• 6 monthly cost: £4,578 (source: AR) |
| Marketing authorisation | Marketing authorisation |
| Treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. | 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. |

# Treatment pathway

**Systemic pathway** for patients with:
- Bilateral + active systemic
- Unilateral + active systemic
- Bilateral + no active systemic (via either pathway)

**Local pathway** for patients with:
- Unilateral or asymmetric bilateral + no active systemic
- Bilateral + no active systemic (via either pathway)

1st line: systemic steroids — **DEX licensed**

1st line: periocular steroids (may repeat) — **DEX licensed**

2nd line: Immunosuppressants (may also continue steroids ≤7.5mg/d):
- One: mycophenolate mofetil (or methotrexate)
- Two: mycophenolate mofetil (or methotrexate) + tacrolimus (or cyclosporine) **VISUAL trials**

**DEX and ADA licensed**

2nd line: Dexamethasone implant (may repeat) — **HURON trial** **DEX licensed**

3rd line: Anti-TNF's (adalimumab, infliximab, etanercept) — **DEX and ADA licensed**

Recreated using Figure 2 in Assessment Report.

# Trial results from company submissions

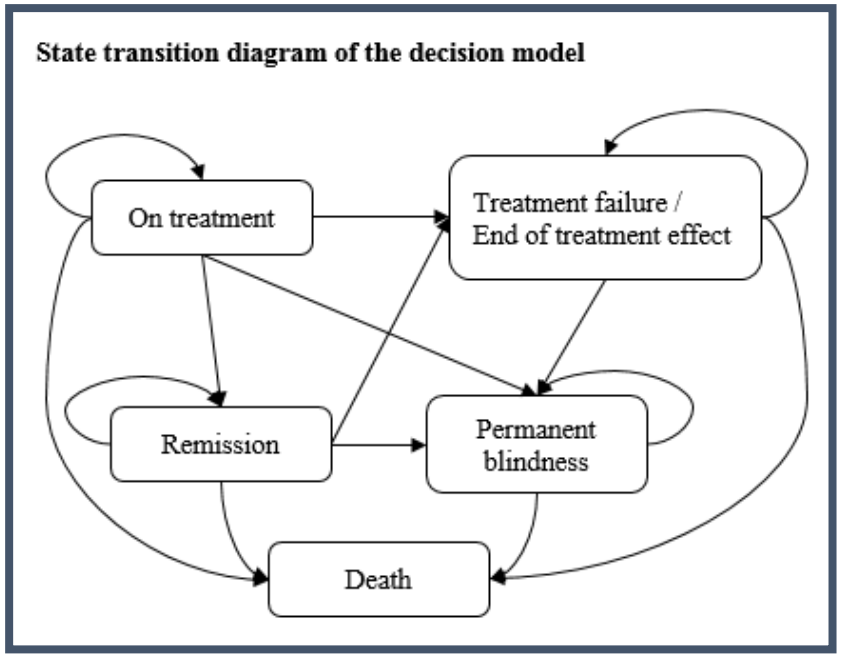
| | Adalimumab vs. placebo (95% confidence interval) | | Dexamethasone vs. sham (95% CI) |
|---|---|---|---|
| **Outcome** | **VISUAL I** | **VISUAL II** | **HURON** |
| **Time to treatment failure*: HR** | **0.50 (0.36 to 0.70)** | **0.57 (0.39 to 0.84)** | **Not reported** |
| **Vitreous haze=0: RR (week 8* and 26)** | **Not reported** | **Not reported** | **Week 8*= 4.0 (2.0 to 7.6)** Week 26= 2.2 (1.1 to 4.1) |
| Mean change in visual acuity: MD | -0.07† (-0.11 to -0.02) | -0.04‡ (-0.08 to 0.01) | MD Not reported, p=0.002 at week 26 |
| Vitreous haze (VH)**: MD | -0.27 (-0.43 to -0.11) | -0.13 (-0.28 to 0.01) | Week 8: -0.97, p<0.001 Week 26: -0.58, p<0.001 |
| Macular oedema (change in thickness µm): MD | Not reported | Not reported | Week 8: -87.0 (-147 to -27) Week 26: -14.7 (-66 to 37) |
| Visual Functioning Questionnaire-25 (VFQ-25) (composite): MD | 4.20 (1.02 to 7.38) | 2.12 (–0·84 to 5·08) | MD Not reported, p=0.001 |

Abbreviations: HR hazard ratio; RR relative risk; MD mean difference
*Primary outcomes; ** VISUAL: Mean change in VH; HURON: Mean VH score

# Assessment group (AG) report

- Companies did not submit cost effectiveness models
- Indirect comparison not appropriate (for example differences in baseline therapy, unknown bilateral uveitis in HURON, differences in rescue therapy in HURON)
- AG Markov model
  - 3 separate analyses based on evidence (active and inactive disease for adalimumab and active disease for dexamethasone)
  - Can't distinguish bilateral and unilateral (>90% in VISUAL trials with bilateral disease)

# AG Model




Source: Figure 7 in AG report

Patients receiving dexamethasone: assumed to have active disease
Patients receiving adalimumab: active and inactive (assessed separately)

- Rates of transition defined from trials (apart from remission and blindness)
- Rate of blindness 0.0066 (Dick et al 2016) in base case
- Blindness utility 0.38 (Czoski-Murray 2009) in base case and 0.57 (Brown et al 1999) in exploratory analyses
- QoL in each health state from trials (EQ-5D for adalimumab, VFQ-25 for dexamethasone & AG mapped to EQ-5D). Both assumed to capture QoL associated with AE during treatment
- Base case assumes no one in remission (exploratory analyses)

# AG Base case

| Base case | Total QALYs | Total costs | Inc. QALYs | Inc. costs | ICER |
|---|---|---|---|---|---|
| **Active uveitis – dexamethasone** | | | | | |
| Clinical practice | 14.613 | £39,655 | - | - | - |
| Dexamethasone plus clinical practice | 14.641 | £40,235 | 0.029 | £580 | **£20,058** |
| **Active uveitis – adalimumab** | | | | | |
| Clinical practice | 14.919 | £47,186 | - | - | - |
| Adalimumab plus clinical practice | 15.110 | £65,401 | 0.191 | £18,215 | **£95,506** |
| **Inactive uveitis – adalimumab** | | | | | |
| Clinical practice | 15.244 | £48,111 | - | - | - |
| Adalimumab plus clinical practice | 15.361 | £85,462 | 0.116 | £37,351 | **£321,405** |

# AG exploratory analyses

1) Background blindness rate
   - 0.0066 (Dick et al 2016) used in AG base case
   - 0.0038 (Tomkins-Netzer et al 2014) used in exploratory analyses
   - 0.0374 (Durrani et al 2004) UK based study used in exploratory analyses
2) Relative risk of blindness for dexamethasone
   - Vary the relative risk of blindness from 0 (no one goes blind while on treatment) to 1 (blindness rate same as comparator)
   - Base case 0.5 (blindness rate 50% lower in DEX vs. comparator)
3) Remission for adalimumab (not included in base case)
   - Assume after 2 years on ADA (stable disease) some patients stop treatment because in remission and maintain same benefits
   - AG exploratory analyses include annual rate either 0, 0.05, 0.1, 0.2 or 1

# Committee preferred assumptions

| Model parameter | Committee preferred assumption |
|---|---|
| Rate of blindness | • 0.0066 acceptable for unilateral disease<br>• 0.0374 where higher risk of blindness (bilateral disease with macular oedema as proxy) |
| Rate of remission | Likely to be some remission after treatment with adalimumab |
| Cost blindness | <£7,700 per year |
| Blindness utility | • 0.57 for all patients (Brown et al 1999) |

# AG exploratory analyses: adalimumab

| Rate of remission* | ICER (no blindness before treatment failure) |
|---|---|
| **Blindness rate of 0.0374 (Durrani et al 2004)** | |
| 0 | £33,003 |
| 0.05 | £25,171 |
| 0.1 | £20,821 |
| 0.2 | £15,994 |
| 1 | £6,942 |
| **Blindness rate of 0.0066 (Dick et al 2016)** | |
| 0 | **£95,506** |
| 0.05 | £77,414 |
| 0.1 | £67,363 |
| 0.2 | £56,214 |
| 1 | £35,299 |
| *Annual rate of patients going into remission and discontinuing treatment whilst maintaining the benefit, if remaining on treatment at 2 years | |

# AG exploratory analyses: dexamethasone

| Annual blindness rate | ICER when varying relative risk of blindness from 0 (no blindness before treatment failure) to 1 (no effect) | | | | |
|---|---|---|---|---|---|
| | RR =0 | RR=0.25 | RR=0.5* | RR=0.75 | RR=1 |
| **Blindness utility of 0.38 (base case, Czoski-Murray et al. 2009 )** | | | | | |
| 0 (no blindness) | £48,937 | £48,937 | £48,937 | £48,937 | £48,937 |
| 0.0066[a*] | £8,688 | £13,314 | **£20,058*** | £30,805 | £50,627 |
| 0.0038[b] | £17,100 | £21,816 | £28,089 | £36,844 | £49,915 |
| 0.0374[c] | Dominates | Dominates | £557 | £10,900 | £56,329 |
| **Blindness utility of 0.57 (Brown et al. 1999)** | | | | | |
| 0 (no blindness) | £48,937 | £48,937 | £48,937 | £48,937 | £48,937 |
| 0.0066[a*] | £12,108 | £17,782 | **£25,257*** | £35,550 | £50,627 |
| 0.0038[b] | £22,015 | £26,972 | £32,988 | £40,440 | £49,915 |
| 0.0374[c] | Dominates | Dominates | £853 | £15,198 | £56,329 |

| | | | | | |
|---|---|---|---|---|---|
| **High cost of blindness (upper bound of 95%)** | | | | | |
| 0 (no blindness) | £48,937 | £48,937 | £48,937 | £48,937 | £48,937 |
| 0.0066[a*] | £6,283 | £11,174 | **£18,305*** | £29,668 | £50,627 |
| 0.0038[b] | £15,195 | £20,185 | £26,822 | £36,085 | £49,915 |
| 0.0374[c] | Dominates | Dominates | Dominates | £8,534 | £56,329 |

*base case; [a] Dick et al 2016; [b]Tomkins-Netzer et al 2014; [c]Durrani et al 2004

# ACD: Preliminary recommendations for adalimumab

1.1 Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is:

- active disease, that is, current inflammation in the eye
- macular oedema
- inadequate response to immunosuppressants
- systemic disease or both eyes are affected and
- worsening vision with a risk of blindness.

# ACD: Preliminary recommendations for adalimumab (2)

1.2 Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following:

- new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both
- *Failure to reduce* anterior chamber cell grade of 0.5+ or less
- *Failure to reduce* vitreous haze grade of 0.5+ or less
- worsening of best corrected visual acuity by 3 or more lines or 15 letters.

# ACD: Preliminary recommendations for dexamethasone

1.3 Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is:

- active disease, that is, current inflammation in the eye and
- macular oedema.

# ACD conclusions: clinical effectiveness

| Section | ACD conclusion |
|---|---|
| 4.2 | In clinical practice, treatment depends on whether disease is:<br>• active (that is, current inflammation in the eye) or inactive (that is, limited inflammation, usually because of treatment with corticosteroids or immunosuppressants)<br>• systemic (when disease is not only in the eye) or non-systemic (when disease is limited to the eye)<br>• unilateral (when 1 eye is affected) or bilateral (when both eyes are affected). |
| 4.6 | Useful to distinguish unilateral from systemic and bilateral disease - people with higher risk of blindness are clinically important subgroup. |
| 4.7 | Both adalimumab and dexamethasone are clinically effective treatments for improving visual acuity, anterior chamber cell grade and vitreous haze. |

# ACD conclusions: cost effectiveness

| Section | ACD conclusion |
|---|---|
| 4.19 | **Adalimumab for inactive disease**<br>• all ICERs >£80,000 per QALY gained<br>• Adalimumab unlikely to be used for inactive disease in clinical practice |
| 4.20 | **Adalimumab for active disease**<br>• More cost effective where high risk of permanent blindness (bilateral disease with macular oedema - useful proxy)<br>• ICERs around £33,000 per QALY gained (probably lower as rate of blindness underestimated for progressive loss of visual acuity). Reasonable to assume some patients in remission<br>• Stopping rule reflects strict criteria for treatment failure (VISUAL I) |
| 4.21 | **Dexamethasone for active disease**<br>• In practice dexamethasone generally used for unilateral disease<br>• ICERs ranged between £25,000 (treat better seeing eye-real risk blindness) and £49,000 per QALY gained (no risk of bilateral blindness but likely to be a significant overestimate as disutility of monocular blindness not modelled)<br>• Committee concluded that the ICER was likely to be within the range normally considered cost-effective |

# Consultation comments

- Companies for adalimumab (AbbVie) and dexamethasone (Allergan)
- Royal college of ophthalmologists (RCO), RNIB, Olivia's Vision (OV), Bird Shot Uveitis Society (BUS), Clinical expert (SS)
- NHS England (NHSE), Health improvement Scotland (HIS), Department of Health and AG
- 1 web response (NHS professional-clinical ophthalmology)

# 1. Recommendation changes (ADA)

- Comment from: RCO, OV, HIS, NHSE, AG

- Recommendations 1.1 to 1.3 need clarification
  - treat based on all criteria or some?
  - add intolerance to immunosuppressants?

# 2. Macular oedema as proxy for blindness? ADA and DEX

- Comment from: RCO, RNBP, Allergan, AbbVie, HIS, NHSE, AG, BUS, SS and web
- Committee concluded people with bilateral disease and macular oedema as a proxy for those at higher risk of permanent legal blindness
- Macular oedema should not be essential criterion for DEX and ADA
  - for ADA captured by 'worsening vision with a risk of blindness'
  - for both ADA and DEX macular oedema is not the only proxy for blindness

# 2. Macular oedema as proxy for blindness? Dexamethasone

- Allergan provide ICERS based on longer re-treatment time (from post authorisation CONSTANCE long term safety study) of 44 weeks (30 weeks in base case) to support removing macular oedema as criterion
- Small risk blindness without macular oedema-likely to be cost effective

| Model changes | ICER vs limited current practice | |
|---|---|---|
| | **Allergan (44 wks*)** | **AG (30 wks*)** |
| 0.57 utility for blindness | £14,016 | £25,257 |
| 0.57 utility and no risk of blindness | £30,898 | £48,937 |
| 0.57 utility for blindness and low risk blindness (0.0038) | £19,658 | £32,988 |
| *Allergan use 44 weeks as DEX treatment effect vs. 30 weeks in AG scenario | | |

# 2. Macular oedema as proxy for blindness? AG response

- Company increase duration of dexamethasone and change blindness to lower rate used in AG exploratory analyses (0.0038) and to 0 suggesting it is somewhere between these values
- AG able to reproduce company's ICERs (technically correct)
- AG question use of CONSTANCE study (no justification over other evidence)
- Papers used for risk of blindness likely to include patient with and without macular oedema. Effectiveness data in model does not differentiate between 2 groups (committee to decide if appropriate to consider patients without MO separately)

# 3. Adalimumab for unilateral disease?

- Comment from: RCO, OV, HIS, NHSE, BUS, SS
- Recommendation for adalimumab shouldn't restrict to bilateral disease
  - occasions where used for unilateral disease (all other criteria fulfilled - local therapy contraindicated/failed or better seeing eye).
  - If uveitis is in better seeing eye, risk of blindness could be as high as bilateral (and therefore, cost-effectiveness the same)

# 4. Stopping rule based on trial too prescriptive? (ADA)

- Comment from: RCO, RNBP, OV, AbbVie, HIS, NHSE, BUS, SS and web

  - Treatment failure in trial not same as clinical practice
  - Single flare of inflammation does not justify stopping adalimumab
  - Suggested using stopping rule from NHS England interim policy

# 5. Use of DEX

- Comment from: RCO, RNIB, OV, Allergan, AG, BUS and web
- Note: issues not included in recommendations but comments suggest clarification in FAD is needed
- More than 3 implants may be used in practice
  - SmPC: Very limited information on repeat dosing intervals less than 6 months. Currently no experience of repeat administrations
- Possible to treat bilateral disease (e.g. where no systemic disease or response to previous treatment, flare up in one eye)

# Key Issues

1. Add intolerance to immunosuppressant?
2. Is macular oedema needed as a proxy?
3. Adalimumab for some unilateral disease (e.g. better seeing eye)?
4. Is stopping rule for adalimumab clinically appropriate?

Potential equality issues in ACD consultation responses

# Proposed changes to recommendations

**Current recommendation (proposed deletions in red and additions in green)**

1.1 Adalimumab is recommended…only if there is:

- active disease, that is, current inflammation in the eye and
- ~~macular oedema~~
- inadequate response or intolerance to immunosuppressants and
- systemic disease or both eyes are affected or the better seeing eye is affected and
- worsening vision with a risk of blindness (for example from macular oedema).

1.2 Stop adalimumab…if there is 1 of the following:

- new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both
- ~~failure to reduce anterior chamber cell grade of 0.5+ or less~~
- failure to reduce vitreous haze grade of 0.5+ or less
- worsening of best corrected visual acuity by 3 or more lines or 15 letters.

1.3 Dexamethasone is recommended…only if there is:

- active disease, that is, current inflammation in the eye and
- worsening vision with a risk of blindness (for example from macular oedema)