Lead team presentation: Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]-Multiple Technology Appraisal

1st Appraisal Committee meeting, 15th February 2017

Background & Clinical Effectiveness

Lead team: Gail Coster and Judith Wardle

Companies: AbbVie (adalimumab) and Allergan (dexamethasone)

For public

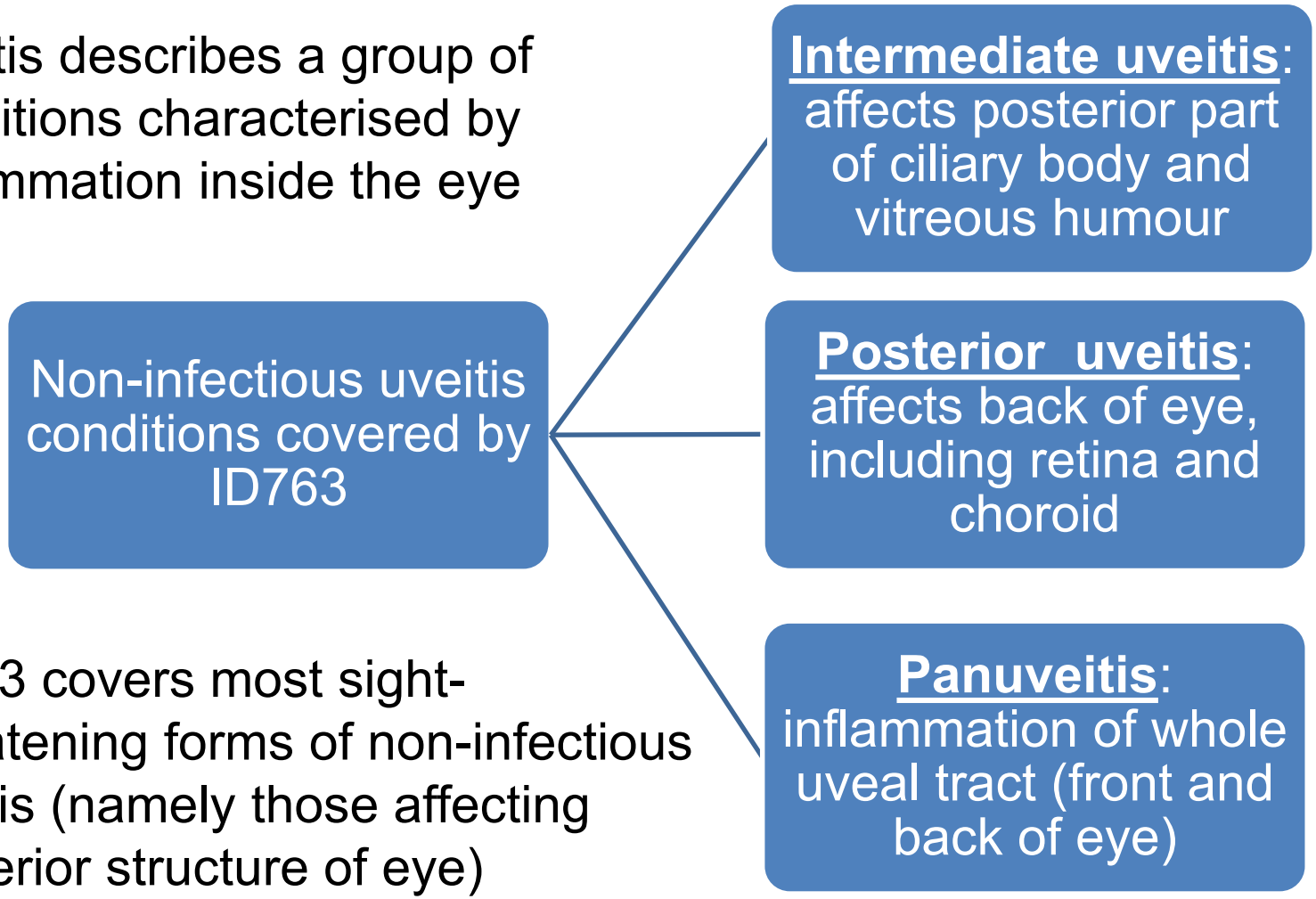
For public

Key issues: clinical effectiveness

- Marketing authorisations vary as follows:
  - Dexamethasone: adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis
  - Adalimumab: 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
- How strong is the clinical efficacy evidence:
  - Trial data only available for both drugs vs either placebo or sham (with some limited use of corticosteroids and immunosuppressants)
  - Does trial comparator reflect clinical practice?
  - AG stated indirect analyses not possible
- How closely does the evidence match the different marketing authorisations for adalimumab and dexamethasone?
- Trials may be too short to capture long-term consequences – do the trials underestimate the long term benefits of interventions?

Disease background non-infectious uveitis (1)

- Uveitis describes a group of conditions characterised by inflammation inside the eye



- ID763 covers most sight-threatening forms of non-infectious uveitis (namely those affecting posterior structure of eye)

Disease background non-infectious uveitis (2)

- Symptoms include blurred vision, ‘floaters’ in eye, pain and redness
- Complications include cystoid macular oedema, vitreous haze, cataracts, glaucoma and irreversible damage to retina
- Generally presents in people aged 20-50
- 5th leading cause of visual impairment in developed countries, accounts for 10% of legal blindness.
- Around 41% to 67% of cases affect both eyes (bilateral)
- Prognosis influenced by underlying cause of uveitis:
  - Posterior and panuveitis associated with more severe visual impairment
  - Panuveitis usually has poorer prognosis than posterior
- Estimated prevalence in England between 1,300 and 4,300

Treatment pathway for uveitis (1)

- No related NICE products (Technology Appraisals, guidance or pathway)
- In clinical practice range of unlicensed immunosuppressants and corticosteroids used
- AG clinical advisors suggest dexamethasone implants and adalimumab used variably in current practice depending on funding
  - Number of patients eligible annually uncertain, company estimates: 589 dexamethasone, 175 adalimumab
- Uveitis is commissioned as a specialist service (not by CCG)
- NHS England does not routinely commission adalimumab for adult patients with severe refractory uveitis*

** Note: Policy also includes infliximab (unlicensed for uveitis). Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/d12pa-infliximab-adalimumab-oct15.pdf*

Treatment pathway for uveitis (2)

non-infectious uveitis (***no nationally agreed 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.
*Pathway based on clinical opinion to AG

NICE Decision problem

	NICE scope	Assessment group
Pop.	People with non-infectious, intermediate, posterior or panuveitis.	As NICE scope but considered active and inactive disease (in line with trial inclusion criteria)
Int.	• Adalimumab subcutaneous injection • Dexamethasone intravitreal implant	
Comp.	• Interventions compared with each other where appropriate • Periocular or intravitreal corticosteroid injections • Intravitreal corticosteroid implants • Systemic corticosteroids • Systemic immunosuppressive therapies and TNF-alpha inhibitor • Intravitreal methotrexate • Best supportive care	Model assessed interventions vs current practice, using trial comparator (placebo or sham with limited use of immunosuppressants & corticosteroids) as: • No direct evidence comparing adalimumab with dexamethasone • Network meta analysis not appropriate (clinical heterogeneity, lack of common comparators and outcomes)
Outcome	visual acuity (the affected eye and both eyes), mortality, adverse effects of treatment, health-related quality of life (VFQ-25 and EQ-5D)	

The technologies

Dexamethasone intravitreal implant	Adalimumab subcutaneous injection
• Ozurdex (Allergan) • 0.7 mg intravitreal implant (biodegradable) in an applicator • Corticosteroid that inhibits pro-inflammatory mediators e.g. cytokines and growth factors (including vascular endothelial growth factor) • £870.00 per implant (BNF Dec 2016) • 6 monthly cost: £870 (source: AR)	• Humira (Abbvie) • 40mg/0.8ml solution for injection every other week • Monoclonal antibody that inhibits the pro-inflammatory cytokine, tumour necrosis factor (TNF)-alpha • £704.28 per two prefilled pens/syringes or vials (BNF Dec 2016) • 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.

Impact on patients and carers

- Complicated condition: inflammation may be + cataract, glaucoma, macular oedema
- Patients isolated – little support
- Greatest impact fear of blindness: also poor quality of life, can't perform normal ADL+ impact on work & family
- Current treatment pathway complicated:
  - Side effects may include night sweats, nausea, fatigue, depression, mood swings, infections if on immunosuppressants.
  - Changes in behaviour difficult for family
  - Many hospital visits
  - Must avoid pregnancy.

Patient/carer views on ADA/DEX

- Both treatments have less compound side-effects than current treatments
  - Trials short & limited range of patients

Adalimumab:

- fewer visits to hospital
- ease of use (but needs refrigeration)
- chance of future pregnancy; “normal life”
- may be preferred if disease bi-lateral

Dexamethasone:

- rapid effect, lasting over 3 months
- some patients may still need steroids: no effect on underlying disease?
- pain of injection in eye: most find tolerable
- only 1 eye treated

Clinical effectiveness summary

- AG carried out systematic review:
- AG focus on 3 trials assessing adalimumab or dexamethasone
- Non-randomised data submitted for dexamethasone (by Allergen) but not adalimumab
- No direct evidence comparing adalimumab with dexamethasone.
- Not possible to carry out indirect comparison

Clinical effectiveness

Included trials

- 3 randomised, international, multicentre (including Europe, North America and Australia) trials:
  - VISUAL I, adalimumab (n=101) vs placebo (n=103), for **active** intermediate, posterior or panuveitis. [redacted] patients from UK
  - VISUAL II, adalimumab (n=115) vs placebo (n=110) for **inactive** intermediate, posterior or panuveitis. [redacted] patients from UK.
  - HURON, dexamethasone implant 0.7mg (n=77) vs sham (n=76), for **active** intermediate and posterior uveitis.
- Active uveitis: current inflammation in the eye.
- Patients with inactive uveitis have limited inflammation, usually due to treatment with corticosteroids or immunosuppressants.
- Trial inclusion criteria provide clinical definitions used for active and inactive uveitis.

Included studies

Baseline characteristics

	Adalimumab vs. placebo		Dex vs. sham
	VISUAL I (n=223) Active uveitis	**VISUAL II (n=229) Inactive uveitis**	**HURON (n=152*) Active uveitis**
Intermediate	22%	21%	81%
Posterior	33%	33%	19%
Panuveitis	45%	46%	None
Bilateral	91%	96%	Not reported
Prior immunosuppressant	32%	48%	25% on systemic immunosuppressant or anti-inflammatory treatment at baseline
Prior corticosteroid	All patients previously taking high dose oral corticosteroids (tapered during trial)		Not reported
Mean duration in months	Adalimumab: 40.2 Placebo: 51.0	Adalimumab: 59.5 Placebo: 62.9	Dexamethasone: 50.5 Sham: 61.2
Follow-up	80 weeks	80 weeks	26 weeks

*n=153 in 0.7mg arms; n=229 in 0.35mg and 0.7mg arms

Treatments used in trials

VISUAL trials

Intervention: adalimumab (80 mg loading then 40mg every other week)

Control: placebo

Concomitant treatment: all taking prednisone (tapered to 0 mg by week 15 in VISUAL I and week 19 in VISUAL II). As needed topical corticosteroids (stopped by week 9) and at least one immunosuppressant.

HURON

Intervention: dexamethasone intravitreal implant, 0.7 mg or 0.35 mg (only use data for 0.7mg in line with SPC)

Control : sham injection

Concomitant treatment: allowed stable dose of corticosteroid, immunosuppressants and topical NSAIDs to be taken as needed. Rescue medication (if VH increased) with intravitreal/periocular

Outcomes measured in trials

Primary outcomes

- VISUAL trials: composite treatment failure outcome, defined as worsening of at least one of the following in ≥1 eye: anterior chamber cell grade, vitreous haze grade, best corrected visual acuity (BCVA), or new active inflammatory retinal or chorioretinal vascular lesions.
  - at 6 weeks or more (VISUAL I) and 2 weeks or more (VISUAL II)
- Huron: proportion of patients with vitreous haze score of zero at week 8 in study eye (also measured up to week 26).

Secondary outcomes (both trials)

- Included vitreous haze grade, anterior chamber cell grade, BCVA, central macular thickness, patient reported outcome (including VFQ-25 and EQ-5D).

Summary results from included trials (1)

	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)
Macular oedema (% change in thickness): MD	-11.4 (-20.9 to -1.8)	-2.3 (-8.5 to 3.8)	Not reported

Abbreviations: HR hazard ratio; RR relative risk; MD mean difference
*Primary outcomes; ** VISUAL: Mean change in VH; HURON: Mean VH score; †Change from best state reached prior to week 6 to final or early termination; ‡From baseline to final or early termination

Summary results from included trials (2)

	Adalimumab vs. placebo (95% CI)		Dexamethasone vs. sham (95% CI)
Outcome	**VISUAL I**	**VISUAL II**	**HURON**
Time to macular oedema in ≥1 eye*: HR	0.70 (0.39 to 1.26)	0.75 (0.34 to 1.69)	Not reported
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
VFQ-25 (>5 point improvement): MD	Not reported	Not reported	MD Not reported, p<0.05
EQ-5D: MD	0.04 (0.00 to 0.07)	0.00 (-0.03 to 0.04)	Not reported
Proportion requiring rescue medication: MD	Not reported	Not reported	MD Not reported, p=0.030

Abbreviations: HR hazard ratio; RR relative risk; MD mean difference
*Change from best state reached prior to week 6 to final or early termination
Visual Functioning Questionnaire-25

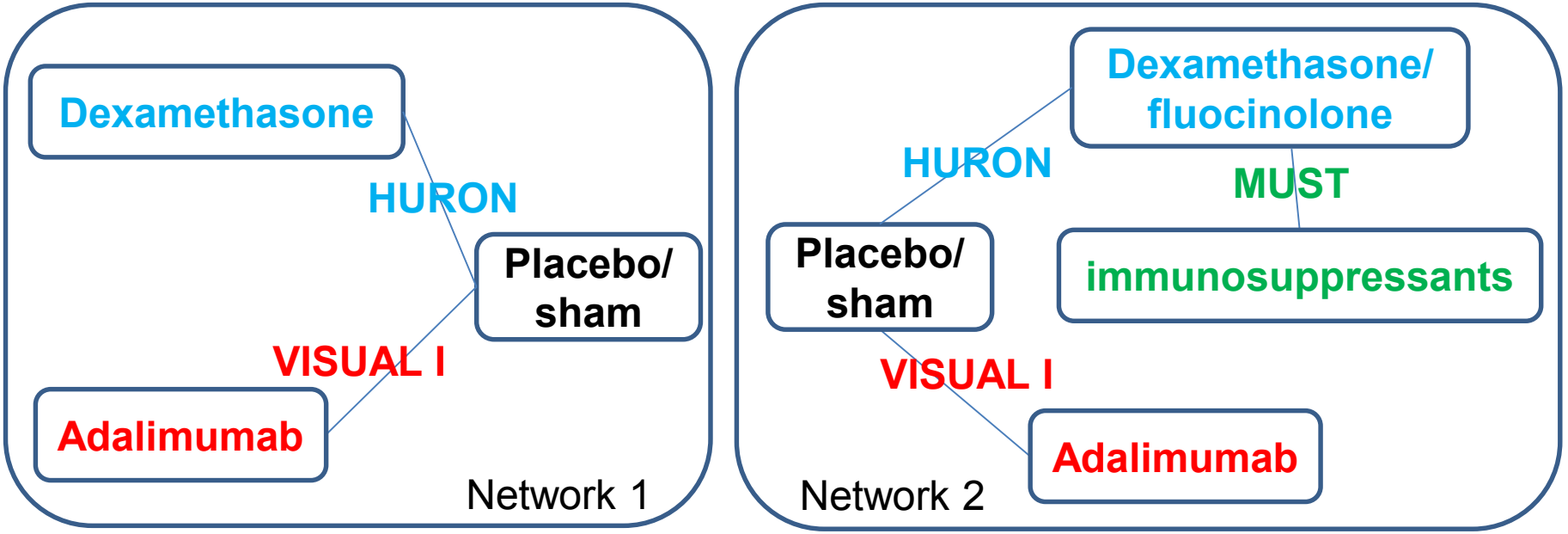
Adverse events

- Adverse events measured over maximum of 80 weeks in VISUAL I (median 19 weeks in adalimumab group and 13 in placebo) and VISUAL II (median 35 weeks in adalimumab and 22 in placebo) and 26 weeks in HURON.

Adverse event	VISUAL I		VISUAL II		HURON	
	ADA %	Placebo % n=112	ADA % n=115	Placebo % n=114	Dex % n=76	Sham n=75
All events	84.7%	78.6%	91.3%	84.2%	80.3%	68.0%
All treatment related*	ADA 40.5% Steroid 51.4	ADA 31.3% Steroid 47.3	ADA 55.7% Steroid 43.5	ADA 45.6% Steroid 42.1	60.5%	28.0%
Serious	13.5%	4.5%	6.1%	7.9%	9.21%	6.7%
Serious treatment related	ADA 5.4% Steroid 1.8	ADA 1.8% Steroid 1.8	ADA 1.7% Steroid 0%	ADA 1.8% Steroid 2.6	NR	NR
Stopped due to adverse events	9.9%	3.6%	8.7%	6.1%	2.6%	0%

*considered possibly treatment-related; NR, Not reported; ADA, Adalimumab; DEX, dexamethasone

Indirect comparison not appropriate



AG highlight differences in:

- Baseline systemic therapy (25% of patients in HURON vs all in VISUAL I)
- Unknown proportion of bilateral uveitis in HURON (≥91% in VISUAL trials)
- Rescue therapy between dexamethasone and sham arm in HURON (no difference in concomitant therapy in VISUAL I)
- Baseline treatments: in VISUAL I all patients were given initial corticosteroid
- Issues with comparability of dexamethasone and fluocinolone CCS implants (Network 2 only)

AG notes on outcome measures (1)

- Visual acuity may reflect degree of intraocular inflammation and extent of damage in the eye
  - inflammation may vary over short time periods (days or weeks)
  - damage may accrue slowly (months or years) and usually irreversible (with exception of cataract and acute cystoid macular oedema).
- Trials capture short-term effects on vision (may be too short to capture long-term consequences and underestimate treatment effect)
- Markers of structural damage to the eye e.g. macular oedema (swelling of the retina), cataract and glaucoma, important because can lead to vision loss, and are objective.
  - may not be good markers of whether treatment reduces inflammation because structural damage may not resolve when inflammation treated.

AG notes on outcome measures (2)

Clinical experts to assessment group suggest:

- VISUAL strict treatment failure criteria means proportion remaining on adalimumab likely to be underestimated
- for ‘inactive’, adalimumab more likely to be used in patients who have to discontinue existing immunosuppressants (ineffective or not tolerated), but no data for this group
- no RCT evidence to assess comparative effectiveness or safety of >1 dexamethasone implant, either in both eyes or consecutively
- adalimumab and dexamethasone likely to be provided alongside other treatment options in practice (unclear if relative treatment effect would stay same if more concomitant therapy added to both arms).

Consultation comments on AR

NICE received 7 responses from AbbVie, Allergan, Department of Health (no comment), NHS England (no comment), Birdshot Uveitis Society, Olivia's Vision and Royal National Institute of Blind People.

AbbVie

- Pan-uveitis not included as subgroup (highest risk of unmanageable disease-recurrent or persistent inflammation)
- Limited literature review (narrow therapeutic area, VISUAL III non-randomised extension of VISUAL trials to report July 2017)

Patient groups

- No 3rd line therapy routinely funded for uveitis and in 2015 NHS England closed IFR route to adalimumab for adult uveitis patients without 2nd condition
- For severe disease, visual acuity is important and if improved from baseline then mental health often also improves

Key issues: clinical effectiveness

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Lead team presentation: Adalimumab and dexamethasone for treating non-infectious uveitis [ID763]-Multiple Technology Appraisal

1st Appraisal Committee meeting, 15th February 2017

Cost Effectiveness

Lead team: Andrea Manca

Companies: AbbVie (adalimumab) and Allergan (dexamethasone)

For public

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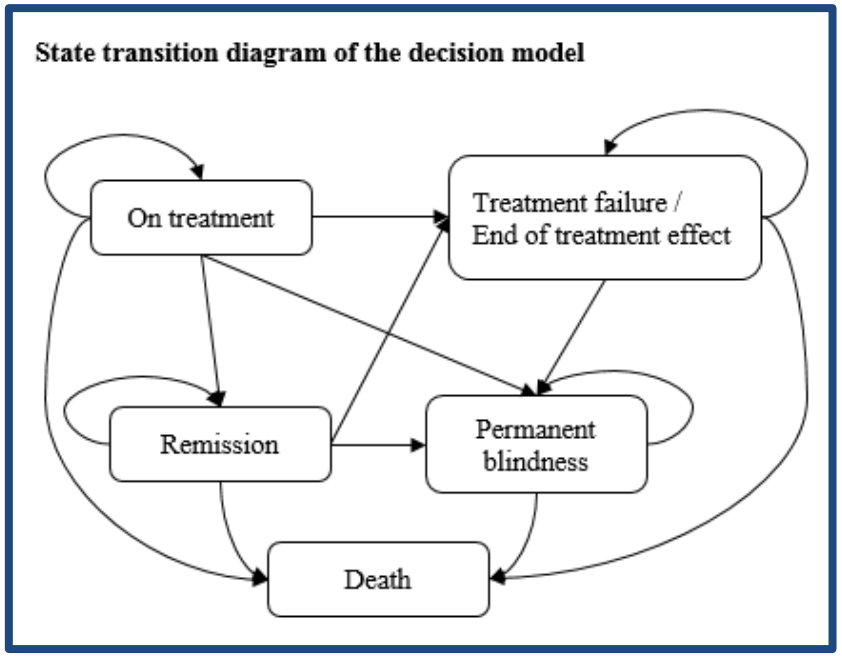
Key issues: Cost-effectiveness

- Do base cases reflect clinical practice (efficacy from trial evidence, often unclear prior therapies and assumed to reflect 2nd line)
- Do model populations reflect current practice (in dexamethasone trial cannot distinguish between unilateral and bilateral disease)? Should different recommendations be made for unilateral and bilateral disease?
- Current treatment is associated with substantial treatment-related morbidity. Has the model adequately captured this?
- The following have large impacts on the ICERs; which assumptions are most appropriate?
  - Adalimumab and dexamethasone: blindness rate, and relative risk of blindness
  - Adalimumab: proportion of patients taken off adalimumab following remission and maintaining the same quality of life
- Adalimumab base case and most scenarios have ICER >£30,000 per QALY gained; are scenarios for increased blindness and remission combined plausible where ICERs are<£30,000 or <£20,000 per QALY gained?
- Can treatments be recommended at a particular line of therapy?

AG Cost-effectiveness model
Comparators

- Dexamethasone and adalimumab compared independently with current practice
- Current practice: immunosuppressants such as methotrexate, mycophenolate mofetil, cyclosporine and azathioprine, and corticosteroids.
  - Costs for these drugs and effectiveness assumed to be equivalent to the control arm (sham or placebo) of the trials
  - Trial placebo/sham arms included relatively low use of corticosteroids or immunosuppressants (for use as rescue therapy only). AG therefore refers to this as limited current practice
- In current practice, greater proportion of patients likely to receive systemic immunosuppressants or anti-inflammatory treatment compared with control arms of included trials (included in scenario analysis)

AG Model structure



Source: Figure 7 in AG report

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

- AG developed Markov model with 5 health states
- For dexamethasone, treatment is one implant (effective 6 months)
- No indirect comparison of dexamethasone with adalimumab as trials not similar enough to be pooled
- Base case assumes no one in remission (exploratory analyses)
- During treatment HRQoL (VFQ-25 or EQ-5D) can improve with treatment effect or lower adverse events
- Lifetime time horizon, 2 week cycles and discounted at 3.5%

Transition (1): Treatment discontinuation in AG model

- Stopping treatment with adalimumab:
  - stop if new inflammatory lesions or worsening of AC cell grade, VH grade or visual acuity (from VISUAL trials)
  - parametric survival curve of time to treatment failure fitted to VISUAL I and II data.

- Stopping treatment with dexamethasone:
  - patients only given 1 implant to 1 eye
  - 30 weeks efficacy assumed (HURON trial).

- After discontinuation, no additional health gains, and patients stay on limited current practice

Transition (2): Permanent legal blindness in AG model

- Trials short and none reported any permanent legal blindness.
  - Treatment can either prevent or increase (via AEs) blindness
- Base case uses constant blindness rate (annual rate 0.0066) associated with current practice in placebo arms.
  - Exploratory analyses used annual rates of
    - 0.0038 (clinical input to AG suggested rate may be underestimated and include a wider population than scope)
    - 0.0374 (includes wider population than scope and patients from tertiary referral centre-more likely to have severe disease)
  - for adalimumab patients cannot go blind before treatment failure (both intervention and comparator).
  - for dexamethasone assume that half of blindness cases can be avoided while treatment is effective (30 weeks in base case).

Transition (3): Other in AG model

Transition to remission (*adalimumab only*)

- State added after clinical advice; assumes adalimumab treatment discontinued after stable period, but benefits continue until failure (from extrapolated curves)
- Only considered in exploratory analyses; not enough evidence for base case

Transition to death

- Mortality rates assumed to reflect general population (ONS)
- Adverse events have no impact on mortality, although AG noted in practice diabetes, osteoporosis, and blindness would impact

Health related quality of life (HRQoL) in AG model

- Mean baseline utility values (based on trial patient level EQ-5D):
  - Dexamethasone 0.79; Adalimumab (active) [redacted] & inactive: [redacted]
- Utility values over time:
  - Adalimumab: EQ-5D data directly from VISUAL
  - Dexamethasone: VFQ25 from HURON mapped to EQ5D using ordinary least squares regression.
- VFQ-25 and EQ-5D data from trials assumed to capture quality of life impacts associated with adverse events during treatment period.
- For blindness utility values taken from literature:
  - Base case: utility of 0.38 (may overestimate utility because source has no utility values for worst states of blindness)
  - In scenario, utility of 0.57 (included valuations by patients with range of conditions associated with blindness)

Treatment costs in AG model

Category	Drug	Dose	6-monthly cost (BNF)	Details
Intervention	Adalimumab	40 mg every 2 weeks	£4,578	
	Dexamethasone	One 0.7 mg implant	£870	
Immuno-suppressant	Mycophenolate mofetil	1g twice daily	£136	Costs weighted average of all treatments based on usage in relevant trial (AG modelled costs of additional immunosuppressants only)
	Methotrexate	15 mg weekly	£16	
	Cyclosporine	2 mg per kg twice daily	£985	
	Azathioprine	1 mg per kg daily	£27	
Corticosteroid with concomitant treatment	Systemic prednisolone	7.5 mg daily	£12	Costs based on systemic prednisolone (AG not model additional costs as trial use similar & inexpensive)
	Adcal D3	20mg daily	£47.58	
	Omeprazole	20mg daily	£15.25	

Source: AR Table 34 and 37 (p118 and 123)

Adverse event costs in AG model (1)

- Trial data used to calculate additional costs for adverse events

- AG only included events with substantial cost as advised by clinical experts
  - cataracts, raised intra ocular pressure, glaucoma, serious infections, hypertension, fractures and diabetes
- Incidence of diabetes and fracture assumed to be similar between treatment and comparator; these are included in exploratory analysis only.

- AG noted benefit of corticosteroid sparing treatment should be incorporated because associated with significant morbidity.
  - But only considered in exploratory analyses, because VISUAL trials do not allow corticosteroids following initial use and HURON suggests minimal difference in usage between groups

Adverse event costs in AG model (2)

Adverse event	Resource use	Cost	Frequency	Source
Cataract	Cataract surgery	£852.40	One off	NHS RC 2014-15
Raised intra ocular pressure	Two doses of bimatoprost	£23.42	One off	BNF, 2016
Glaucoma	Glaucoma surgery	£581.25	One off	NHS RC 2014-15
Serious infection	Hospitalisation	£5,940.50	One off	NHS RC 2014-15
Hypertension	Anti-hypertensive prescription	£7.04	One off	Breeze et al.
Fracture	Hospitalisations, accident and emergency visits, referrals, prescriptions and GP contacts	£2,116.17 to £6,022.62*	One off	Davis et al. 2016
Diabetes	Annual diabetes treatment and hospitalisation for complications of diabetes	£1,521.46	Annual	UKPDS study† (Alva et al. 2015) Breeze et al.

*depending on age and gender, † largest study of the costs of diabetes and complications in the UK

Adverse event costs in AG model (3): Blindness

- Literature search for cost data limited from 2006 and most recent good quality evidence associated with costs of blindness from HTA of treatment for age related macular degeneration (Colquitt et al 2008)

Resource use	Patients	Cost	Source
Blind registration*	95%	£146	Meads et al. 2003
Low vision aids*	33%	£191	Meads et al. 2003
Low vision rehabilitation*	11%	£329	Meads et al. 2003
Depression	39%	£2,378	McCrone et al. 2008
Hip replacement	5%	£4,086	NHS Reference costs 2014-2015
Community care	6%	£281	PSSRU 2015, social care for older people
Residential care†	30%	£21,732	PSSRU 2015, private residential care
Annual total		**£7,659**	
Transition to permanent blindness		**£237**	

Key: *, one-off; †, 30% of residents pay themselves.
Source: AR Table 35 and 36 (p120)

Other costs in AG model

Administration and monitoring

Parameters	Mean	Distribution	Source
Monitoring visit frequency	6 weeks	NA	Jabs et al.
Monitoring visit cost	£96.11	Gamma	NHS Reference costs 2014-15, outpatient attendance, ophthalmology, consultant-led
Dexamethasone implant administration cost	£113.42	Gamma	NHS Reference costs 2014-15, Minor Vitreous Retinal Procedures
% people self-injecting adalimumab needing district nurse	10%	Beta	TA375
Adalimumab administration cost (help from a nurse)	£44	Gamma	PSSRU 2015, district nurse

Source: AR Table 37 (p123)

AG base-case cost effectiveness results

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**

- Probabilistic ICERs for all treatments were similar to deterministic
- Probability of cost effectiveness at £20,000 to £30,000 per QALY gained:
  - Dexamethasone: 47% and 72% respectively
  - Adalimumab for active and inactive: 0% both

Source: AR Table 39 and 40 (p129)

AG Scenario analyses (1)

Scenario	ICER vs limited clinical practice		
	DEX	**Adalimumab (active)**	**Adalimumab (inactive)**
AG base case	**£20,058**	**£95,506**	**£321,405**
1. Increased immunosuppressants and corticosteroids in comparator groups	£19,899*	£109,044*	Not reported
2. Use HRQoL VFQ25 mapped to EQ-5D	NR	£92,884	£348,094
3. Alternative parametric curves for time to treatment stopping (base case uses Log normal)	NR	£101,429 and £103,369	£297,746 and £235,916
4. Change duration of dex treatment effect from 30 weeks to 26 weeks	£24,715	Not reported	Not reported
5. Duration of treatment effect 42 weeks	£12,154	Not reported	Not reported

Abbreviations: DEX dexamethasone; NR not reported *from probabilistic analyses, †lower ICERs associated with rate 1.00.

AG Scenario analyses (2) Blindness

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

AG Scenario analyses (3) Blindness

Adalimumab-active uveitis

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)	£192,808	£192,808	£192,808	£192,808	£192,808
0.0066[a*]	**£95,506***	£110,263	£129,611	£156,077	£194,471
0.0038[b]	£121,908	£134,773	£150,325	£169,503	£193,740
0.0374[c]	£33,003	£44,570	£63,587	£100,494	£202,592
Blindness utility of 0.57 (Brown et al. 1999)					
0 (no blindness)	£192,808	£192,808	£192,808	£192,808	£192,808
0.0066[a*]	**£119,012***	£132,539	£148,886	£169,031	£194,471
0.0038[b]	£142,399	£152,827	£164,646	£178,154	£193,740
0.0374[c]	£48,876	£63,923	£86,679	£124,952	£202,592
High cost of blindness (upper bound of 95%)					
0 (no blindness)	£192,808	£192,808	£192,808	£192,808	£192,808
0.0066[a*]	**£93,765***	£108,775	£128,453	£155,372	£194,422
0.0038[b]	£120,637	£133,725	£149,546	£169,056	£193,712
0.0374[c]	£30,187	£41,936	£61,245	£98,713	£202,352

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

AG Scenario analyses (4) Blindness

Adalimumab-inactive uveitis

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)	£4,814,459	£4,814,459	£4,814,459	£4,814,459	£4,814,459
0.0066[a*]	**£321,405***	£420,805	£607,928	£1,089,865	£5,133,625
0.0038[b]	£527,056	£679,863	£956,162	£1,606,857	£4,988,973
0.0374[c]	£85,544	£112,594	£167,837	£331,006	£7,411,362
Blindness utility of 0.57 (Brown et al. 1999)					
0 (no blindness)	£4,814,459	£4,814,459	£4,814,459	£4,814,459	£4,814,459
0.0066[a*]	**£514,958***	£665,947	£940,350	£1,593,079	£5,133,625
0.0038[b]	£821,798	£1,040,149	£1,414,808	£2,206,843	£4,988,973
0.0374[c]	£141,538	£185,892	£275,797	£536,245	£7,411,362
High cost of blindness (upper bound of 95%)					
0 (no blindness)	£4,814,459	£4,814,459	£4,814,459	£4,814,459	£4,814,459
0.0066[a*]	**£318,140***	£417,608	£604,860	£1,087,124	£5,133,625
0.0038[b]	£523,933	£676,848	£953,341	£1,604,491	£4,988,973
0.0374[c]	£82,177	£109,245	£164,519	£327,767	£7,411,362

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

AG Scenario analyses (5) Remission

- Assume after 2 years on adalimumab (stable disease), some patients stop treatment because in remission and maintain same benefits of treatment
- All ICERs >£35,000 per QALY gained
- Only ICER <£36,000 per QALY gained assumes 100% of patients stop treatment because in remission after 2 years on adalimumab

	ICER when varying annual rate of stopping treatment			
	0 (base case)	**0.10**	**0.25**	**1.00**
Active uveitis	£95,506	£67,363	£52,707	**£35,299**
Inactive uveitis	£321,405	£199,031	£142,832	£84,132

AG Scenario analyses (6) remission and blindness combined for adalimumab-active uveitis

Rate of remission*	ICER when varying relative risk of blindness from 0 (no blindness before treatment failure) to 1 (no effect) and remission				
	RR =0	**RR=0.25**	**RR=0.5**	**RR=0.75**	**RR=1**
Blindness rate of 0.0374 (Durrani et al 2004)					
0	£33,003	£44,570	£63,587	£100,494	£202,592
0.05	£25,171	£35,800	£53,081	£86,392	£178,191
0.1	£20,821	£30,708	£46,738	£77,576	£162,462
0.2	£15,994	£24,866	£39,237	£66,867	£142,883
1	£6,942	£13,443	£23,995	£44,308	£100,230
Blindness rate of 0.0066 (Dick et al 2016)					
0	**£95,506**	£110,263	£129,611	£156,077	£194,471
0.05	£77,414	£90,126	£106,777	£129,541	£162,547
0.1	£67,363	£78,848	£93,889	£114,448	£144,253
0.2	£56,214	£66,261	£79,419	£97,403	£123,473
1	£35,299	£42,476	£51,876	£64,726	£83,353

*Annual rate of patients going into remission and discontinuing treatment whilst maintaining the benefit, if remaining on treatment at 2 years

AG Univariate sensitivity analyses

- Univariate sensitivity analyses for parameters including utility values, administration and monitoring, and adverse event costs
  - Dexamethasone: All ICERs <£26,000 per QALY gained
  - Adalimumab for active disease: All ICERs >£88,602 per QALY gained
  - Adalimumab for inactive disease: All ICERs >£270,000 per QALY gained

Innovation

- Company for dexamethasone summarise innovations:
  - pharmacokinetic benefits as drug is cleared rapidly from the eye,
  - Other routes of administration require much higher daily doses of dexamethasone to achieve therapeutic levels in the posterior segment of the eye while exposing non-target areas of the body to corticosteroids
  - allows localised treatment of the eye without need for regular injections
  - reduction in systemic exposure to corticosteroids
- Company's submission for adalimumab does not refer to innovation.

Potential equality issues

- Company for dexamethasone state that equality impact of recommendations for those patients for whom vision may be reduced or lost in one eye already may need to be assessed, as this group is at risk of becoming sight disabled.
- Company submission for adalimumab does not refer to equality issues.

Consultation comments on AG report

AbbVie raised concerns about:

- Vision loss rates – AG base case should use higher rate (Durrani most realistic)
- Remission not included in base case model (exploratory analysis stopping treatment >2 years reasonable assumption)
- Using direct EQ-5D data for ADA (EQ-5D insensitive to visual impairment – should map VFQ-25 to EQ-5D)
- Age at start of the model (44.8) from HURON only (should also use VISUAL trials, 42.7 and 42.5 years)
- Impact of vision loss (not blindness) and disease flares on vision loss not included
- Exclusion of costs for optical correction by spectacles post-cataract surgery for steroid-related cataract formation and indirect costs of blindness

Consultation comments on AG report

Allergan

- Risk of blindness likely to be between estimates from Dick et al (2016) and Durrani et al (2004)
- Dex treatment effects would continue post treatment end (30 weeks)
  - reduces irreversible damage by controlling macular oedema therefore would have lasting effect on risk of blindness
  - Duration of treatment effect varies by patient – quality of life benefits can continue >30 weeks
- AG model does not include malignancies for patients receiving standard care despite this risk for patients receiving long-term immunosuppressants
- Substantial non-NHS costs and benefits excluded.

Patient groups

- Living with sight loss at working age substantially increases cost of living.
- Substantial patient benefit from both medications (rare diseases) but difficult to quantify meaningfully.
- Model does not reflect different degrees and progressions of visual impairment.

Key issues: Cost-effectiveness

- Do base cases reflect clinical practice (efficacy from trial evidence, often unclear prior therapies and assumed to reflect 2nd line)
- Do model populations reflect current practice (in dexamethasone trial cannot distinguish between unilateral and bilateral disease)? Should different recommendations be made for unilateral and bilateral disease?
- Current treatment is associated with substantial treatment-related morbidity. Has the model adequately captured this?
- The following have large impacts on the ICERs; which assumptions are most appropriate?
  - Adalimumab and dexamethasone: blindness rate, and relative risk of blindness
  - Adalimumab: proportion of patients taken off adalimumab following remission and maintaining the same quality of life
- Adalimumab base case and most scenarios have ICER >£30,000 per QALY gained; are scenarios for increased blindness and remission combined plausible where ICERs are<£30,000 or <£20,000 per QALY gained?
- Can treatments be recommended at a particular line of therapy?