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DEXAMETHASONE IMPLANT FOR NON-INFECTIOUS UVEITIS: IS IT COST-EFFECTIVE?

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SYNOPSIS:

The dexamethasone implant for adult patients with non-infectious posterior segment-involving uveitis is estimated to be cost-effective using generally accepted UK thresholds. However, there is substantial uncertainty around these results and further primary research is recommended.

ABSTRACT

Background

Uveitis is inflammation inside the eye. The objective of this study is to assess the cost-effectiveness of a dexamethasone implant plus current practice (immunosuppressants and systemic corticosteroids) compared with current practice alone, in patients with non-infectious intermediate, posterior or pan-uveitis and to identify areas for future research.

Methods

A Markov model was built to estimate the costs and benefits of dexamethasone. Systematic reviews were performed to identify available relevant evidence. Quality of life data from the key randomised-controlled trial (HURON) was used to estimate the interventions' effectiveness compared with the trial's comparator arm (placebo plus limited current practice (LCP)). The analysis took a National Health Service and Personal Social Services perspective. Costs were calculated based on standard UK sources.

Results

The incremental cost-effectiveness ratio (ICER) of one dexamethasone implant compared with LCP is estimated as £19,509 per quality-adjusted life year (QALY) gained. The factors with the lar**g**est impact upon the results were rate of blindness and relative proportion of blindness cases avoided by dexamethasone. Using plausible alternative assumptions, dexamethasone could be cost saving, or it may be associated with an ICER of £56,329 per QALY gained compared with LCP.

Conclusions

Dexamethasone is estimated to be cost-effective using generally accepted UK thresholds. However there is substantial uncertainty around these results due to scarcity of evidence. Future research on the following would help provide more reliable estimates: effectiveness of dexamethasone versus current practice (instead of LCP), with subgroup analyses for unilateral and bilateral uveitis; incidence of long term blindness; and effectiveness of dexamethasone in avoiding blindness.

INTRODUCTION

Uveitis is a group of conditions characterised by inflammation inside the eye. Complications of uveitis including cystoid macular oedema, vitreous haze, cataracts, glaucoma, and irreversible damage to the retina may lead to loss of vision. Uveitis generally presents in people of working age and accounts for 10% of cases of legal blindness, defined here as best-corrected visual acuity of 20/200 or less in the better-seeing eye and/or a visual field of 20 degrees or less.[1]

Dexamethasone intravitreal implant (Ozurdex, Allergan) is a corticosteroid implant which suppresses inflammation by inhibiting the expression of pro-inflammatory mediators. Dexamethasone implant has a marketing authorisation from the European Medicines Agency (EMA) for treating adults with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.[2] The prevalence of non-infectious posterior segment-involving uveitis is estimated to be between 3 and 10 out of 100,000 people.[2]

Non-infectious posterior segment-involving uveitis is usually treated with corticosteroids first line, which may be administered systemically or locally. Long-term use of systemic corticosteroids above 7.5mg per day is not recommended due to the side effects which include cataract, glaucoma, diabetes, osteoporosis, weight gain and raised blood pressure. Second line treatment is typically immunosuppressive drugs including methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus and azathioprine, and these can allow a reduction in the corticosteroid dose and associated complications. It is expected that dexamethasone implant could provide an alternative second line option for patients who have unilateral uveitis or asymmetric bilateral uveitis, where systemic disease is not present or is well-controlled.

However, national funding bodies need to know if dexamethasone implants are cost-effective in order to inform recommendations for clinical practice. To our knowledge, this is the first economic evaluation of the dexamethasone implant in patients with non-infectious uveitis. The objective of this study is to assess the cost-effectiveness of dexamethasone compared with current practice in England in patients with non-infectious intermediate, posterior or panuveitis and to identify areas for future research.

METHODS

A systematic review of existing economic evaluations was undertaken of the dexamethasone implant for non-infectious uveitis. Since no relevant economic evaluations were identified from the review, a de novo economic model was developed. Systematic reviews were also undertaken of the effectiveness evidence and utility estimates which have been described elsewhere.[3]

Health Economic Model Scope

The model population consists of adults with active non-infectious intermediate, posterior or pan uveitis, with a mixture of unilateral and bilateral uveitis.

The comparator is current UK practice, which for the main analysis is assumed to be equivalent to the control arm of the main randomised controlled trial of the dexamethasone implant, HURON.[4] In this group, 25% of patients were using systemic immunosuppressants (such as methotrexate, mycophenolate mofetil, cyclosporine and azathioprine) or anti-inflammatory treatment at baseline and they were allowed rescue therapy with new corticosteroids or immunosuppressants. In current UK practice, a greater proportion of patients are likely to receive systemic immunosuppressants or anti-inflammatory treatment than in the control arm of the HURON trial. As such the comparator for the main analysis is denoted throughout as limited current practice based on HURON (LCP(H)). An exploratory analysis was also undertaken to assess the impact of alternative baseline effectiveness, based on the comparator of the Multicentre Uveitis Steroid Treatment (MUST) trial.[5] A systematic review was undertaken which found no other evidence of the effectiveness of the dexamethasone implant from a randomised controlled trial. Observational studies of the implant have been reported and these are discussed later; however they do not provide evidence of the relative impact of dexamethasone. The intervention being assessed is one 0.7mg dexamethasone implant provided in one eye, plus LCP(H), to be consistent with the HURON trial.[4]

The main outcome of the model is the incremental cost per quality-adjusted life year (QALY) gained for dexamethasone compared with current practice. QALYs are estimated by assigning a health-related utility value to each health state in the model, where 0 is equivalent to death and 1 is equivalent to full health, and summing these over the patients' lifetime. The incremental cost per QALY gained is the difference in costs associated with the dexamethasone implant and current practice divided by the difference in QALYs associated with the dexamethasone implant and current practice. This outcome allows the cost-effectiveness of dexamethasone to be compared against other healthcare interventions for different populations and indications. The analysis is performed from a National Health Service (NHS) and Personal Social Services (PSS) perspective and costs and QALYs are discounted at a rate of 3.5% per year as recommended by the National Institute for Health and Care Excellence (NICE),[6] since this work was used to inform a decision about how to spend NHS and PSS resources.[7] An accompanying model of adalimumab for this population was also developed to inform the same NICE guidance, which is reported elsewhere.[8][9]

Health Economic Model Design

A Markov model was developed, which simulates a cohort of patients through a set of mutually exclusive health states, with probabilities of moving between the states every time cycle. Patients enter the model with a mean age of 44.8, based on HURON,[4] and are followed over a lifetime.

There are four health states: (i) dexamethasone implant, no blindness; (ii) no dexamethasone implant, no blindness; (iii) blindness; and (iv) death, as shown in Figure 1. Patients in the dexamethasone implant group start in the "dexamethasone implant, no blindness" state and move to the "no dexamethasone implant effect, no blindness" state after 30 weeks. Patients in the comparator group begin immediately in the "no dexamethasone implant effect, no blindness" state. Each 2-weekly cycle, patients have a probability of experiencing permanent damage to the eye, transitioning to "blindness". Patients can also transition to the "death" state. Treatment benefit is represented with higher health-related quality of life (HRQoL) and lower rates of condition-related adverse events whilst in the "dexamethasone implant, no blindness" state, as well as a reduced risk of permanent blindness. The health states of the model were chosen to reflect the events which were thought to have the largest impact upon costs and quality of life. Searches were undertaken around the disease natural history of blindness for uveitis patients to inform the transitions between health states.

Model inputs

Model inputs were taken from a variety of sources. A summary of these parameters are included in Table 1.

Table 1: Model input parameters for the base case analysis

Parameters	**Mean**	**Distribution used in PSA**	**Source**
Starting age (active/inactive)	44.8	Fixed	HURON [4]
Discount rate (costs and utilities)	3.5%	Fixed	NICE Reference Case [6]
Gender (% males)	36.7%	Fixed	HURON [4]
Cycle length	2 weeks	Fixed	
Utilities			
Baseline VFQ-25 for the dexamethasone implant and LCP(H)	66.63	Beta	HURON [4]
Blindness utility	0.38	Multivariate normal	Czoski-Murray *et al*. [10]
Proportion of uveitis patients with bilateral disease in the UK	75%	Beta	Expert clinical opinion
Proportion of uveitis patients with bilateral disease in the HURON trial	70%	Beta	Combination of patient level data from the HURON trial [4] and clinical opinion
Probability of blindness (annual)	0.0068	Beta	Dick *et al.* [11]

Parameters	Mean	Distribution used in PSA	Source
Relative risk of blindness for dexamethasone versus no implant during 6 month period following implantation	0.5	Uniform	Assumption
Drug costs			
Dexamethasone 0.7mg	£870	Fixed	BNF, 2016[12]
Prednisolone	£1.24	Fixed	BNF [13]
Mycophenolate mofetil	£9.31	Fixed	BNF [13]
Methotrexate	£2.40	Fixed	BNF [13]
Cyclosporine	£48.50	Fixed	BNF [13]
Azathioprine	£3.24	Fixed	BNF [13]
Bimatoprost	£11.71	Fixed	BNF [13]
Adcal D3	£7.49	Fixed	BNF [13]
Omeprazole	£1.17	Fixed	BNF [13]
Administration and monitoring			
Monitoring visit frequency	6 weeks		Jabs *et al.* [14]
Monitoring visit cost	£96.11	Gamma	NHS Reference costs 2014-15[15]
Dexamethasone implant administration cost	£113.42	Gamma	NHS Reference costs 2014-15, Minor Vitreous Retinal Procedures[15]
Costs of adverse events			
Cataract surgery	£852.40	Gamma	NHS Reference costs 2014-15 [15]
Raised intraocular pressure	£23.42	Gamma	BNF [13]
Glaucoma procedure	£581.25	Gamma	NHS Reference costs 2014-15[15]
Hypertension	£7.04	Gamma	Breeze et al. [16]
Blindness (transition)	£237	Gamma	Colquitt *et al.* [17]
Blindness (annual)	£7,659	Gamma	Colquitt *et al.* [17]
Fracture	£2,116.17-£6,022.62	Gamma	Davis *et al.* [18]
Diabetes	£1,521.46	Gamma	Alva *et al.* [19], Breeze *et al.* [16]

Health-related quality of life

The VFQ-25 health-related quality of life (HRQoL) outcome was used because it captured most fully the positive and negative effects of the implant. The use of visual acuity and vitreous haze outcomes within the model were also considered, however the VFQ-25 was preferred because of the difficulties associated with capturing all impacts of the dexamethasone implant using one visual outcome. The HURON trial [4] reports VFQ-25 health-related quality of life (HRQoL) data at baseline and at each follow-up visit.

Another HRQoL measure that was collected at baseline within the trial was the five dimensional EuroQol (EQ-5D) measure, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This is a standardised instrument which is considered to be the gold standard in order to compare HRQoL across a wide range of health conditions and treatments. It is necessary to convert VFQ-25 data to EQ-5D utilities in order to estimate QALYs, as required by NICE in order to enable a comparison of the cost-effectiveness of all interventions across different patient populations. The manufacturer of the dexamethasone implant, Allergan, shared patient-level data from the HURON trial with the project team which allowed an analysis of the relationship between VFQ-25 and EQ-5D using the baseline data.

A linear regression model was fitted to the data from HURON to predict EQ-5D utilities from the VFQ-25, as shown in Figure 2, assuming that the relationship is independent of treatment:

$$\text{EQ-5D utility} = 0.4454059 + \text{VFQ-25 score} * 0.0051322$$

Alternative non-linear models (eg. quadratic regression) were also tested but did not significantly improve the fit to the data.

The utility for patients entering the model was set to be the same for both the dexamethasone implant group and the comparator by calculating the average VFQ-25 from these two arms of the HURON trial, and using the linear regression to predict the EQ-5D utility. Utility over time was estimated using the VFQ-25 data from the HURON trial at 8, 16 and 26 weeks, adjusted by the baseline VFQ-25, to predict EQ-5D at these time points using the linear regression.

Permanent blindness

A goal of the use of the dexamethasone implant is to prevent permanent damage to the eye. It was therefore important to include a rate of blindness and the impact of dexamethasone upon that rate. However, this outcome was not captured by the HURON trial due to its short duration.[4] Given the lack of evidence, only blindness in both eyes was incorporated into the model. A study by Dick *et al.*[11] was used to estimate the rate of blindness for people with uveitis receiving current care. This was a retrospective analysis of insurance claims data (n=1769) where all patients had posterior segment, non-infectious uveitis, and provided an estimate of 6.6% of patients going blind within 10 years. Two other sources were also identified and were used in sensitivity analyses; Tomkins-Netzer *et al.,*[20] which included a wider population than our target population (including patients with infectious and anterior uveitis) and, Durrani *et al.,*[21] based on a tertiary referral centre. It was assumed that the dexamethasone implant could halve the number of cases of blindness over the 6 months that it is effective. Since there is no evidence about this parameter, it was varied within sensitivity analyses.

The utility associated with the "blindness" health state was taken from a study by Czoski-Murray *et al.*[10] who used contact lenses to simulate blindness associated with age-related macular degeneration.

Adverse events

Given that quality of life data were used directly to model treatment effectiveness, it was assumed that the impact on quality of life associated with adverse events (AEs) whilst on treatment would be already captured. Therefore, only the additional costs associated with the management of AEs were modelled and the AEs included within the model are limited to those where the cost of treatment is substantial: cataract, raised intraocular pressure, glaucoma, serious infections; hypertension; fractures; and diabetes. The probabilities for AEs per cycle were calculated based on the incidence and mean follow-up in the HURON trial.

Costs

The model includes treatment costs, administration costs and monitoring costs, as well as adverse event costs and the cost of permanent blindness, as shown in Table 1. The model assumes that all patients would receive monitoring every 6 weeks, irrespective of treatment, consisting of outpatient visits to assess the efficacy of the treatments and to monitor the risk of AEs. It is assumed that patients receiving immunosuppressants would have 6 additional blood monitoring visits annually.

Model analysis

Probabilistic sensitivity analyses (PSA) were run using Monte Carlo simulation with 5,000 samples. This allows for non-linearity in the model and incorporates distributions around each model input parameter to capture the uncertainty around their true value, leading to an estimate of the uncertainty in the model results. Deterministic results have also been produced which simply use the best estimate for each parameter in the model. Due to the scarcity of appropriate evidence on key model parameters, a range of exploratory analyses were undertaken in order to assess the impact of alternative assumptions upon the model results. Where deterministic and probabilistic central results are similar, the deterministic model can be used within exploratory analyses to reduce model run time.

For more details on the model, please refer to the corresponding HTA report.[3]

RESULTS

The key model results are presented in Table 222 and Table 3. A single dexamethasone implant combined with limited current practice as provided in the HURON trial (DEX + LCP(H)) was estimated to result in a probabilistic ICER of £19,509 per QALY gained compared with LCP (H). However, there is substantial uncertainty around this result. Based on the uncertainty around the

model parameters, there is an estimated 72% chance that the dexamethasone implant will be a good use of resources if the decision maker is willing to pay £30,000 for each QALY gained.

Given the paucity of evidence, a number of alternative assumptions have been tested within exploratory analyses to assess their impact upon the model results. The first exploratory analysis considers a comparator which is more representative of current UK practice than the comparator arm of HURON. The comparator arm of the MUST trial[5] (identified within the systematic review), is made up of patients who received systemic corticosteroids, supplemented in 86% of the cases with immunosuppressants and is thought to be reasonably representative of UK clinical practice. Data from this trial was used for: (a) an estimate of the total proportion of patients receiving (i) corticosteroids and (ii) immunosuppressants in order to estimate costs; (b) an estimate of the HRQoL of patients, and; (c) the rates for any adverse events associated with substantial resource use. It is assumed within this exploratory analysis that patients treated with dexamethasone are also able to receive immunosuppressants and corticosteroids. This analysis results in both arms being associated with greater costs and greater QALYs, whilst the incremental ICER remains similar (see Table 2).

Whilst the observational studies undertaken to date suggest that the treatment effect of dexamethasone is around 6 months, there is some uncertainty around this, with some studies suggesting time to treatment failure may be longer. As such, the second exploratory analysis varies the length of the treatment effect of the dexamethasone implant (see Table 2) from 26 weeks to 42 weeks. The ICER for DEX + LCP(H) versus LCP(H) varies from £12,154 to £24,715 per QALY gained.

Table 22: Model results

	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER	Probability of cost-effectiveness at WTP threshold	
						£20,000	£30,000
Main results (probabilistic)							
LCP(H)*	14.599	£39,992				0.53	0.28
DEX + LCP(H)*	14.629	£40,565	0.029	£573	£19,509	0.47	0.72
Main results (deterministic)							
LCP(H)*	14.613	£39,655				N/A	N/A
DEX + LCP(H)*	14.641	£40,235	0.029	£580	£20,058	N/A	N/A
Exploratory analysis 1: comparing dexamethasone with arm from the MUST trial (probabilistic)							
CP(M)**	15.152	£63,465				0.54	0.45
DEX + LCP(H)* before CP(M)**	15.163	£63,681	0.011	£216	£19,899	0.47	0.55
Exploratory analysis 2: varying duration of treatment effect (deterministic)							
LCP(H)	14.613	£39,655				N/A	N/A
Dex:26 weeks	14.637	£40,256	0.024	£600	£24,715	N/A	N/A
Dex:30 weeks*	14.641	£40,235	0.029	£580	£20,058	N/A	N/A
Dex:34 weeks	14.646	£40,214	0.033	£559	£16,692	N/A	N/A

Dex:42 weeks	14.655	£40,173	0.043	£518	£12,154	N/A	N/A

*LCP(H)= Limited current practice, as provided in the HURON trial:25% of patients on anti-inflammatory or immunosuppressant medication.
**CP(M)= Current practice as provided in the MUST trial: all patients on systemic steroids and 86% on systemic immunosuppressants.

The third exploratory analysis varies the rate of blindness for patients receiving current care at the same time as varying the relative risk of blindness when receiving dexamethasone. Table 3 shows the resulting incremental cost per QALYs gained. These results show that the impact of dexamethasone upon blindness is a key model parameter and as such model results can range from dexamethasone being cost saving to having a cost per QALY above the currently accepted thresholds for cost-effectiveness within England. For example, if the current rate of blindness is taken from the study by Durrani *et al.*[21] and dexamethasone has no effect on the rate of permanent blindness then the dexamethasone implant is estimated to have a cost per QALY gained of £56,329 compared with current practice. Longer term research is needed to reduce the uncertainty around this parameter and hence around the model results.

Table 3: ICERs when varying rate of blindness and relative risk of blindness on dexamethasone

Source	**Rate of blindness (annual)**	**RR of blindness whilst on dexamethasone**				
		0 (no blindness)	**0.25**	**0.50***	**0.75**	**1 (no effect)**
Assumption	0	£48,937	£48,937	£48,937	£48,937	£48,937
Tomkins-Netzer et al.[20]	0.0038	£17,100	£21,816	£28,089	£36,844	£49,915
Dick et al.[11]*	0.0066	£8,688	£13,314	£20,058*	£30,805	£50,627
Durrani et al.[21]	0.0374	Dominates	Dominates	£557	£10,900	£56,329

*main result
'Dominates' means that the dexamethasone is estimated to be more effective and less costly than current care

The HURON trial did not provide outcomes separately for patients with bilateral and unilateral disease; however these exploratory results suggest that the dexamethasone implant may not be considered to be cost-effective, using standard thresholds of cost-effectiveness in England, in patients with unilateral disease since it will not prevent blindness in these patients. However, patients may later go on to develop uveitis in the second eye, and hence by preserving vision in the first eye the implant may prevent future blindness, thus improving cost-effectiveness in this group.

In addition to the above analysis, each of the key model parameters was modified individually within plausible ranges to test their impact upon the model results. The only other parameter which impacted the ICER by more than £2,000 was the utility associated with blindness. This utility was changed from 0.38 (Czoski-Murray *et al.*[10]) to 0.57 (Brown *et al.*[22]) which resulted in a deterministic ICER of £25,257 per QALY gained for dexamethasone plus LCP(H) compared with LCP(H).

DISCUSSION

The HURON study presented outcomes at 26 weeks and no patients went blind within the trial period, making the model predictions about the proportion of patients going blind over the long term highly uncertain. Research around how short-term improvements in visual acuity or inflammation relate to long-term effects on moderate to severe vision loss and blindness would provide more robust estimates of the cost-effectiveness of dexamethasone.

The model assumes that only one dexamethasone implant would be provided to patients. There are several non-randomised studies with 12–24 months follow up, which allow repeat implants.[23-25] These studies suggest that after around six months, patients' outcomes return to those at baseline and second and third implants are associated with effects similar to first implants. Each additional implant is associated with a higher incidence of adverse events such as intraocular pressure (IOP) and cataract,[23-25] and this would limit repeated use. The univariate sensitivity analyses suggested that the model is not sensitive to the cost of IOP or cataract, and hence, given that the cost of each implant is the same, the cost-effectiveness of up to three consecutive implants is expected to be similar to the cost-effectiveness of one implant. The ICER would be expected to decrease if there was also a cumulative impact upon the reduction in blindness or if patients were to achieve remission after consecutive implants.

There is insufficient evidence to assess the cost-effectiveness of using dexamethasone implants in both eyes for a patient with bilateral disease. However, because the costs would essentially be doubled (with the exception of some monitoring costs) and the increment in HRQoL is likely to be lower for the second eye, it is expected to be less cost-effective than treatment in one eye.

This analysis takes a NHS and PSS perspective as required by NICE and does not include broader societal impacts such as productivity loss. NICE produced guidance,[7] informed by this analysis, that dexamethasone is recommended in the NHS as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with active disease and worsening vision with a risk of blindness. However, considerable uncertainty remains due to lack of evidence on the long-term treatment effect (such as avoiding permanent blindness and visual impairment), on the prevalence of permanent blindness and visual impairment in the target population and on utility values after the onset of blindness. There is a serious unmet need to gather more primary data in this area to support health economic decisions in uveitis without which inappropriate resource allocation decisions are more likely to be made.

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COMPETING INTERESTS STATEMENT

The authors have no competing interests that are directly relevant to the content of this article.

CONTRIBUTORSHIP STATEMENT

Hazel Squires led the project and advised on the cost-effectiveness modelling. Inigo Bermejo undertook the cost-effectiveness review and developed the cost-effectiveness model. Edith Poku and Katy Cooper undertook the clinical effectiveness review. John Stevens and Jean Hamilton commented on statistical issues and feasibility of network meta-analysis and Ruth Wong performed the literature searches. Alastair Denniston, Ian Pearce and Fahd Quhill provided clinical advice. All authors were involved in drafting and commenting on the manuscript.

FIGURE LEGENDS

Figure 1: State transition diagram of the decision model

Figure 2: The relationship between VFQ-25 and EQ-5D based on patient-level data from the HURON trial

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