A systematic review and economic evaluation of adalimumab and dexamethasone for treating non-infectious intermediate uveitis, posterior uveitis or panuveitis in adults

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Scientific summary

Treating adults with non-infectious intermediate, posterior or panuveitis

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Scientific summary

Background

Uveitis describes a group of conditions characterised by inflammation of the uveal tract. The underlying cause may be infectious or non-infectious. In the UK and the developed world, uveitis is most commonly non-infectious and likely autoimmune in origin, either isolated to the eye or associated with systemic autoimmune disorders. This study covers the most sight-threatening forms of non-infectious uveitis, those affecting the posterior structures of the eye, termed intermediate uveitis (vitreous humour and posterior ciliary body), posterior uveitis (retina and choroid) and panuveitis (front and back of the eye). It does not cover anterior uveitis (iris and anterior ciliary body). Symptoms include blurred vision, floaters and sometimes pain and redness. Consequences leading to potential vision loss include early complications such as cystoid macular oedema (retinal swelling) and vitreous haze (VH) (inflammatory cell debris in the vitreous) and late complications such as cataracts (lens cloudiness), glaucoma [optic nerve damage from increased intraocular pressure (IOP)] and irreversible retinal damage. Between 3 and 16 in 100,000 people are estimated to have non-infectious posterior segment-involving uveitis. Uveitis generally presents in working-age people, is the fifth leading cause of visual impairment in developed countries and accounts for 10% of cases of legal blindness.

Current treatment includes corticosteroids (systemic or local injection or implant) as first-line treatment and immunosuppressive drugs (such as methotrexate, mycophenolate mofetil, ciclosporin, tacrolimus and azathioprine) as second-line treatment for uveitis unresponsive to corticosteroids or which recurs on steroid tapering. Tumour necrosis factor (TNF)-alpha inhibitors are considered a third-line option. The majority of these treatments are not currently licensed. The technologies assessed in this study were adalimumab (ADA) (Humira®; AbbVie Ltd, Maidenhead, UK), a monoclonal antibody TNF-alpha inhibitor, and dexamethasone (DEX) (Ozurdex®; Allergan Ltd, Marlow, UK), a corticosteroid intravitreal implant.

Aims

The aims of this study were to:

- evaluate the clinical effectiveness and safety of ADA (via subcutaneous injections) and a DEX intravitreal implant within their marketing authorisations for non-infectious intermediate uveitis, posterior uveitis or panuveitis in adults
- estimate the incremental cost-effectiveness of ADA and a DEX intravitreal implant for non-infectious intermediate uveitis, posterior uveitis or panuveitis compared with each other and current treatment
- estimate the expected overall cost of ADA and DEX treatment in England
- identify areas for primary research.

Methods

Searches of nine databases to June/October 2016 including MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) identified randomised controlled trials (RCTs) of ADA, DEX implants and relevant comparators. Study quality was assessed using the Cochrane risk-of-bias tool. Results were synthesised using narrative synthesis. The use of a network meta-analysis (NMA) was explored.

Searches were undertaken for existing cost-effectiveness studies in non-infectious uveitis. A de novo Markov model was developed by the Assessment Group (AG) to assess the cost-effectiveness of DEX and ADA, each compared with (limited) current practice, from a NHS and Personal Social Services (PSS) perspective over a lifetime horizon. The two interventions were not compared directly as they are often used in different patient scenarios and, when comparison would be clinically appropriate, there was insufficient trial evidence. The cost-effectiveness of ADA was assessed separately for active and inactive uveitis and the cost-effectiveness of DEX was assessed only for active uveitis. The model included five health states: (1) treatment: no permanent blindness, (2) treatment failure: no permanent blindness, (3) permanent blindness, (4) remission and (5) death. Effectiveness was modelled using EuroQol-5 Dimensions (EQ-5D) utility data from the ADA trials and by regression analysis, mapping scores from the 25-item Visual Function Questionnaire (VFQ-25) reported within the DEX trial to EQ-5D utilities. Health-related quality of life (HRQoL) (VFQ-25 or EQ-5D) could be improved by a reduction in inflammation, improvements in vision or a reduction in adverse events (AEs). Treatment may reduce the risk of permanent damage to the eye, resulting in a decreased risk of legal blindness. Given the uncertainties around the comparators and long-term outcomes, substantial exploratory and sensitivity analyses were undertaken.

Results

Of the 134 full-text articles screened, three studies (four articles) were included in the clinical effectiveness review. Two RCTs compared ADA (40 mg every 2 weeks by subcutaneous injection) with placebo: VISUAL I (active uveitis, $n = 223$) and VISUAL II (inactive uveitis, $n = 229$). Over 90% of patients had bilateral uveitis. As ADA is a systemic treatment, both eyes were treated. All patients were on high-dose corticosteroids at baseline and patients in the VISUAL I trial received an initial high-dose steroid burst; steroids were then tapered in both studies. One concomitant immunosuppressant was received by 30% of participants in the VISUAL I trial and 47% of participants in the VISUAL II trial. Follow-up was carried out up to 80 weeks or until treatment failure and outcomes were measured from the best response following the steroid burst (VISUAL I) or from baseline (VISUAL II) to treatment failure or the study end. One RCT of DEX implants (HURON, $n = 229$) compared a dose of 0.7 mg (DEX 700) or 0.35 mg (DEX 350) with a sham procedure over 26 weeks. This assessment was limited to the licensed DEX 700 group compared with the sham group. One eye per patient received a single implant (right eye if bilateral; worse-seeing eye in 84% of all patients). Systemic therapies were received by 25% of participants at baseline and could be continued throughout the trial. The proportion of bilateral cases was not recorded. Thirteen additional trials of clinically relevant comparator treatments [vs. placebo or one another as per the National Institute for Health and Care Excellence (NICE) scope] were identified. However, pairwise meta-analysis and NMA were not feasible because of clinical heterogeneity, lack of common comparators (the network was disconnected) and differences in reported outcomes.

Clinical effectiveness

The primary outcome for the VISUAL trials of ADA was treatment failure, defined as worsening of any of the following in either eye: anterior chamber (AC) cell grade, VH grade, best corrected visual acuity (BCVA) or new inflammatory lesions. In the VISUAL I trial (active uveitis), the median time to treatment failure was 5.6 months in the ADA arm compared with 3.0 months in the placebo arm [hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.36 to 0.70; $p < 0.001$]. In the VISUAL II trial (inactive uveitis), the median time to treatment failure was not estimable in the ADA arm and was 8.3 months in the placebo arm [HR 0.57, 95% CI 0.39 to 0.84; $p = 0.004$). The VISUAL I trial reported significant benefits for ADA compared with placebo for changes in the following (averaged across both eyes): visual acuity [mean difference (MD) –0.07; $p = 0.003$), VH (MD –0.27; $p < 0.001$), AC cell grade (MD –0.29; $p = 0.011$), macular oedema (percentage change in central retinal thickness: MD –11.4%; $p = 0.020$), VFQ-25 composite score (MD 4.20; $p = 0.010$) and EQ-5D score (MD 0.04; $p = 0.044$). In the VISUAL II trial, differences were not significant for ADA compared with placebo for changes in any of visual acuity (MD –0.04; $p = 0.096$), VH (MD –0.13; $p < 0.070$), AC cell grade (MD –0.14; $p = 0.218$), macular oedema (percentage change in central retinal thickness: MD –2.3%; $p = 0.451$), VFQ-25 composite score (MD 2.12; $p = 0.160$) or EQ-5D score (MD 0.00; $p = 0.836$).

Secondary outcomes in the VISUAL I and II trials were measured only to treatment failure or the study end and, as treatment failure occurred in more patients on placebo than on ADA, the last observation carried forward method may have introduced bias as data post treatment failure were not missing at random.

In the HURON trial there were significant benefits of DEX 700 compared with the sham procedure for the following (measured in the study eye only): percentage of patients with a VH score of zero at 8 weeks (MD 34.9%; $p < 0.001$) and 26 weeks (MD 16.7%; $p = 0.014$), percentage with a VH improvement of ≥ 2 units at 8 weeks (MD not reported; $p < 0.001$) and 26 weeks (MD not reported; $p = 0.001$), percentage with a BCVA improvement of three or more lines at week 26 (MD 24.5%; $p < 0.001$), mean BCVA improvement over weeks 3–26 (no values reported; $p \leq 0.002$), decrease in central retinal thickness at 8 weeks (MD –87.0 µm; $p = 0.004$) although not at 26 weeks (MD –14.7 µm; $p = 0.58$), change in VFQ-25 composite score at 8 weeks (MD 5.4; $p = 0.007$) and 26 weeks (MD 7.3; $p = 0.001$) and percentage of patients with a $\geq$ 5-point improvement in VFQ-25 score at 8 weeks (54.8% vs. 27%; $p < 0.001$) and 26 weeks (57.5% vs. 32.4%; $p < 0.05$). Rescue medications (corticosteroid injections or new/increased use of systemic therapies) were required in 22% of the DEX 700 group compared with 38% of the sham group ($p = 0.030$).

As ADA affects the immune system, potential risks of treatment include infections and malignancy. Serious infections were higher in the ADA group than in the placebo group in the VISUAL I trial (4.5% vs. 1.8%) but not in the VISUAL II trial (1.7% vs. 1.8%). Across both trials, malignancies and chronic renal failure each occurred in three patients in the ADA group, with no cases in the placebo group. Systemic AEs that had a higher rate in the ADA group than in the placebo group in at least one RCT included infections, injection site reactions, fatigue, arthralgia, myalgia, paraesthesia, hypertension and elevated levels of liver enzymes. Anti-ADA antibodies occurred in 2.7% of participants in the VISUAL I trial and 5% of participants in the VISUAL II trial. There was little difference in ocular AEs between the groups.

In the HURON trial, the following AEs were reported: raised IOP (DEX 700 25% vs. sham 7%), IOP of $\geq$ 25 mmHg (DEX 700 7.1% vs. sham 1.4%), glaucoma (DEX 700 0% vs. sham 2.7%), cataracts in phakic eyes (DEX 700 15% vs. sham 7%), endophthalmitis (severe eye infection) (DEX 700 1.3% vs. sham 0%) and conjunctival haemorrhage (DEX 700 30% vs. sham 21%). No systemic AEs had a significantly higher rate in the DEX 700 group than in the sham group.

No patients required incisional surgery, 2.6% of participants in the DEX 700 group required a laser iridotomy and, at any one time, up to 23% of participants in the DEX 700 group required IOP-lowering medication (not reported for the sham group). Cataract surgery was required in 1.6% of participants in the DEX 700 group compared with 3.6% of participants in the sham group.

Cost-effectiveness

The base-case analysis undertaken by the AG estimated the incremental cost-effectiveness ratio (ICER) of one DEX implant in one eye for a combination of patients with unilateral and bilateral uveitis compared with limited current practice, as per the HURON trial, to be £19,509 per quality-adjusted life-year (QALY) gained. The ICER of ADA (systemic, therefore treatment for both eyes) for patients with mainly bilateral uveitis compared with limited current practice, as per the VISUAL trials, was estimated to be £94,523 and £317,547 per QALY gained in active and inactive uveitis respectively.

Exploratory analyses suggested that the two factors that have the largest impact on the ICERs, both highly uncertain, are the rate of blindness in the comparator group and the relative risk of blindness for ADA or DEX compared with the comparator. The ICER for DEX compared with (limited) current practice varied from dominating to £56,329 per QALY gained when varying these parameters. When the rate of legal blindness was set to zero to explore the cost-effectiveness of DEX for unilateral uveitis, the estimated ICER was £50,627 per QALY gained. Under all assumptions tested for these parameters, the ICER for ADA compared with (limited) current practice, based on the VISUAL trials, remained above £30,000 and £82,000 per QALY for active and inactive uveitis respectively. The factor that had the largest impact on the ICER for ADA was the proportion of patients who were assumed to stop ADA treatment following remission and maintain the

same quality of life; assuming that all patients go into remission after 2 years on ADA, the ICER was reduced to £35,299 and £84,132 per QALY for active and inactive uveitis respectively.

Discussion

The results of the economic model are highly uncertain because of the limited evidence base. In addition to the issues explored within the sensitivity analyses, several further differences between evidence and practice were not possible to quantify. First, clinical advisors to the AG (three of the authors, AD, IP and FQ, who provided clinical advice throughout) suggested that the proportion of patients remaining on ADA may be underestimated within the VISUAL trials because of strict criteria for treatment failure. If more people remained on treatment, the additional patients would incur the same costs but experience reduced effectiveness of ADA and hence the ICERs for ADA would increase. Second, clinical advisors suggested that ADA use in 'inactive' patients would be restricted to patients discontinuing immunosuppressants because they are ineffective or not tolerated; however, there are no data for this group. Third, the model assumed the use of only one DEX implant per patient. There is no RCT evidence assessing more than one implant, either in both eyes or consecutively. Although the AG explored the impact of consecutive implants, there were insufficient data to consider the cost-effectiveness of DEX implants in both eyes. However, because costs would essentially be doubled and the HRQoL increase would probably be lower for the second eye, implants in both eyes are expected to be less cost-effective than treatment in one eye only. Fourth, clinical advisors suggested that ADA and DEX are likely to be provided alongside other treatments. In the trials, around one-third of patients in both arms received other treatments. However, it is unclear whether or not the relative effectiveness of ADA and DEX predicted within the trials would remain if the use of alternative treatments in both the intervention group and the comparator group was increased. Finally, because of a lack of evidence for a comparator representing current practice, it is unclear how ADA and DEX may affect the use of other treatments. The model incorporated the impact of DEX on use of rescue therapy, but this was based on the analysis using a sham comparator. If treatment with DEX or ADA led to a reduction in use of immunosuppressants and/or corticosteroids without having an impact on efficacy, then they would be more cost-effective than currently predicted.

The population considered in the model was heterogeneous and the interventions may be more cost-effective in some groups than others. However, there was no trial evidence to facilitate subgroup analyses. Patients with more severe uveitis, such as those with macular oedema, may benefit more from ADA or DEX; hence, the treatments may be more cost-effective as baseline disease worsens. In addition, ADA used to concurrently treat uveitis and systemic symptoms may be more cost-effective than ADA used to treat uveitis alone. The analysis in which the rate of blindness was set to zero, which could be used to explore the cost-effectiveness of DEX for patients with unilateral uveitis, suggested that the ICER compared with (limited) current practice increases substantially.

The analysis presented here takes a NHS and PSS perspective. Non-infectious uveitis affects a working-age population and can affect workplace productivity and leisure time. Therefore, there are likely to be additional non-NHS and non-PSS costs and benefits associated with the treatments that are not captured within our analyses.

Conclusions

Two RCTs of systemic ADA and one RCT of a unilateral single DEX implant showed significant benefits of the treatments compared with placebo or a sham procedure for outcomes including visual acuity, inflammation, macular oedema, VFQ-25 score and time to treatment failure. Use of one DEX implant in a mixed group of unilateral and bilateral patients had an estimated ICER of £19,509 per QALY gained compared with (limited) current practice. The ICER associated with ADA compared with (limited) current practice did not fall below £30,000 per QALY gained in any of the analyses carried out.

There is substantial uncertainty around the evidence, in particular with regard to the comparative effectiveness and cost-effectiveness of DEX and ADA and their effectiveness and cost-effectiveness compared with those of systemic immunosuppressants and corticosteroids and how short-term improvements in visual acuity and inflammation relate to long-term effects on vision loss and blindness. The impact of differences between clinical practice and trial evidence is uncertain. Finally, there is insufficient evidence from patient subgroups in which the interventions may be more or less effective and cost-effective.

Study registration

This study is registered as PROSPERO CRD42016041799.

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