VALUE BASED OPHTHALMOLOGY

Cost utility of photodynamic therapy for predominantly classic neovascular age related macular degeneration

C Hopley, G Salkeld, P Mitchell

Background/aim: Age related macular degeneration (AMD) is the major cause of severe visual impairment affecting older people in the developed world.\(^1\) There are currently around 420 000 older people in the United Kingdom with AMD, of which 214 000 have registrable blindness secondary to AMD.\(^2\) People with vision impairment utilise considerable healthcare resources\(^3\) and frequently use community support services to maintain independent living in the community.\(^5\)

Late AMD presents in two forms: atrophic ("dry") AMD, which usually has a slow onset and rate of progression; and neovascular ("wet") AMD, which is the more virulent form of the disease and is twice as frequent.\(^6\) In neovascular AMD, visual deterioration usually results from choroidal neovascularisation (CNV) at the macula, where new vessels develop and evolve to subretinal fibrosis.\(^7\) CNV is traditionally classified according to: (1) position relative to the fovea: extramacular, juxtapfoveal, and subfoveal, and (2) fluorescein angiographic appearance: "classic," "occult," and "mixed."\(^8\)

There are limited options for the treatment of neovascular AMD. Laser photocoagulation has proved to be effective at treating most forms of CNV, but can only be used effectively when the CNV is extramacular or juxtafoveal in position. It is generally not helpful when the CNV is subfoveal (as the laser energy would destroy the central macula). Although laser photocoagulation is cost effective,\(^8\) it can only be used in approximately 15% of neovascular AMD cases.\(^8\)

Photodynamic therapy (PDT) is a treatment for neovascular AMD using a photosensitising dye (verteporfin) in conjunction with low power diode laser light. In the Treatment of Age-related Macular Degeneration with PDT (TAP) Study,\(^9\) PDT was shown to be clinically effective in decreasing the risk of vision loss (>3 lines) for people with predominantly classic CNV lesions. PDT using verteporfin, however, is currently relatively expensive at around £1284 (A$2670) per treatment.

PDT is currently the only proved therapy for predominantly classic subfoveal neovascular AMD. It has recently completed a lengthy appraisal process and is now funded by the NHS. Other studies have shown PDT to have at best moderate cost effectiveness.\(^10\)\(^12\)

The aim of this study was to model the cost per quality life year saved (QALY) through the use of PDT treatment, in comparison with placebo treatment, and to refine cost effectiveness estimates for the purpose of funding decisions. The study was conducted from a third party payer perspective.

METHODS

Cost utility models were created for the following case scenarios:

Model 1

- Reasonable initial visual acuity (VA) 6/12 in the better seeing eye (approximate visual acuity of one mode of the TAP study); this VA level was used in base case 1 of the Sharma models.\(^11\)
- Predominantly classic CNV in that eye (PDT treatment has proved efficacy)\(^10\)
- Poorer vision in the fellow eye (worse than 6/24)\(^11\)
- Average age 75 years (TAP study average).\(^10\)

Abbreviations: AMD, age related macular degeneration; CNV, choroidal neovascularisation; CUA, cost utility analysis; NICE, National Institute for Clinical Evaluation; PDT, photodynamic therapy; PPP, purchasing power parity; QALYs, quality adjusted life years; VA, visual acuity
Model 2

- Poor initial VA 6/60 in the better seeing eye (approximate visual acuity of one mode of the TAP study); this VA level was used in base case 2 of the Sharma models.
- Predominantly classic CNV in that eye (PDT treatment has proved efficacy).
- Poorer vision in the fellow eye (counting fingers and worse).
- Average age 75 years (TAP study average).

The models incorporated data from the TAP study regarding therapeutic efficacy, Australian life tables regarding expected mortality rates, Blue Mountains Eye Study data regarding the increased mortality associated with AMD, and an AMD related utility valuation. Costs and QALYs were adjusted to the reference year of 2003 using a discount rate of 6%.

TAP study findings

The TAP study was a double masked clinical study comparing PDT treatment for neovascular AMD, with placebo, and has now published data over 3 years. PDT was shown to decrease the absolute risk of developing 3 lines or more vision loss with PDT treatment by 28% (68.7% developed >3 lines vision loss on placebo compared with 40.9% on PDT treatment) on predominantly classic CNV lesions over 2 years. This difference was statistically significant (p<0.001). The open label TAP extension has indicated minimal worsening of vision for the PDT group in year 3, while using an average of 1.3 PDT treatments per patient over that period. The average age of subjects was 75 years.

AMD related utility assessment

The incremental utilities were derived from work of Brown et al. The measurement of utilities was developed to deal with rational decision making when confronted with uncertainty. Utilities, by convention, vary from 1.0 (perfect health) to 0.0 (death). Studies have shown that the utilities associated with ophthalmic disease are most highly correlated with visual acuity in the better seeing eye and exhibit good retest reliability. Visual acuity is more important than the pathological cause of eye disease, as far as ophthalmic utility values are concerned.

AMD related utility values have been established, using time trade-off methodology, for different ranges of best corrected visual acuity in the better eye (Table 1). The incremental decrease in visual acuity (>3 lines), associated with the placebo arm, permits an annual calculation of utilities, and hence QALYs, that accrue because of PDT treatment. We assumed a binary state for the TAP study related visual outcomes: the progression or non-progression of 3 line loss of vision related to the placebo and treatment groups. The incremental utilities associated with these outcomes are 0.24 for people with initial VA 6/12 and 0.12 for people with initial VA 6/60 (Table 1).

Cost identification data

Costs were identified by reviewing the literature, supplemented by expert opinion of AMD resource use, and were measured according to yearly use per affected person. The study included only relevant variable incremental costs (Table 2). Schedule fees were obtained from published 2003 Australian Medicare Benefits Schedule (MBS) data. The MBS is a schedule of fees upon which the government reimburses the providers of medical services. Various other costs such as capital expenditure, overheads costs, and certain labour costs were assumed to be equivalent in both the treatment and placebo arms and were not examined. Indirect costs were also not assessed.

Other data sources and assumptions

Survival data for the cohort were calculated from ABS life tables. These rates were adjusted for sex and the increased mortality associated with AMD (risk ratio 1.7) resulting in a weighted average expected lifespan of 7 years for the average TAP patient (aged 75 years). Australian Federal Government funding for PDT was assumed to be extended over the 7 years modelled. No disutility associated with PDT was modelled owing to the lack of patient based utility values.

Decision analysis and cost utility modelling

Decision analysis was conducted to determine the incremental utilities associated with PDT treatment (Tables 3 and 4). Cost utility analysis was then conducted over a modelled time frame of 7 years. The two alternatives considered in the models were treatment with PDT and placebo treatment. Annual incremental utility values (and hence QALYs) were calculated separately from the associated incremental costs and thereafter combined to derive cost effectiveness ratios.

Model assumptions

The baseline visual acuity was 6/12 in model 1 and 6/60 in model 2. The treatment group (in both models) was modelled to receive the following PDT treatments per year (as per the TAP study): 3.4 in year 1, 2.2 in year 2, and 1.3 in year 3 (as per TAP extension study). The decrease in absolute risk (28%) of having a 3 line diminution in vision associated with treatment, was used to finalise the incremental annual utility values. We assumed that to maintain a constant decreased risk at 28%, repeat treatments averaging 1.0 per annum would be necessary over the patient's remaining lifespan.

Purchasing power parity

Purchasing power parity (PPP) rates were used to convert costs between currencies. Under PPP, exchange rates are adjusted to eliminate the differences in price levels between countries and to better reflect the real value of money when converting the costs of goods and services from one currency to another (www.pacific.commerce.ubc.ca/xt/PPP.html). We used Organisation for Economic Co-operation and Development (OECD) rates (www.oecd.org/std/ppp) to respectively derive the 0.481 and 0.654 factors used to convert Australian dollars and US dollars to pounds sterling in the reference year of 2003.

Discounting

A real discount rate of 6% (UK Treasury rate) was used for both costs and QALYs, as recommended by Drummond et al.
Sensitivity analysis
A preliminary analysis of the models was conducted for the relevant variables, using a fixed percentage change in input values. The variables that most affected the incremental cost effectiveness ratios (cost per QALY) were selected for further evaluation in a one way sensitivity analysis. A range of values reflecting the inherent uncertainty for each selected variable was tested.

RESULTS
Model 1
This is based on initial VA of 6/12 in the better seeing eye, the development of subfoveal predominantly classic CNV, and receiving treatment annually for a total of 7 years (versus placebo). This resulted in an incremental adjusted QALY of 0.395 for a modelled total of 10.9 PDT treatments. The total adjusted cost associated with this utility equalled £12 478, which results in a cost per QALY of £31 607.

Likely variability or suggested fixed values were tested in the one way sensitivity analysis. This resulted in a range of incremental cost effectiveness ratios from £25 285 to £37 928 per QALY. Lowest and highest cost utility ratios were obtained with incremental utility values of 0.3 and 0.2 respectively. Overall, the sensitivity analysis confirmed the model to be robust (fig 1).

Model 2
This is based on initial VA of 6/60 in the better seeing eye, the development of subfoveal predominantly classic CNV, and receiving treatment annually for a total of 7 years (versus placebo). This resulted in an incremental adjusted QALY of 0.197 for a modelled total of 10.9 PDT treatments. The total adjusted cost associated with this utility equalled £12 478, which results in a cost per QALY of £63 214.

Likely variability or suggested fixed values were tested in the one way sensitivity analysis. This resulted in a range of incremental cost effectiveness ratios from £54 183 to £75 856 per QALY. Lowest and highest cost utility ratios were obtained with incremental utility values of 0.14 and 0.10, respectively. Overall, the sensitivity analysis confirmed the model to be robust (fig 2).

DISCUSSION
AMD is the leading cause of severe visual impairment in the developed world and it imparts a significant burden on society. Unpublished data suggest an average annual cost of around A$290 million (£140 million) in Australia, with less than a quarter of the total being immediately attributable to direct clinical costs. There are limited options for decreasing this burden on a society-wide scale. Smoking is the most important modifiable risk factor, with current smokers developing AMD three to four times more frequently and 10 years earlier than non-smokers. The Age Related Eye Disease Study (AREDS) showed that early AMD could be retarded through the use of high dose zinc and antioxidants. We have recently shown that a screening and prophylactic treatment programme using zinc and antioxidants is cost effective.

Once late AMD has developed, conventional laser and PDT are currently the only proved treatments. PDT is funded and available in Australia, and has recently received NHS funding in the United Kingdom. Our cost utility model 1 scenario, assuming a baseline VA of 6/12 and predominantly classic CNV in the better seeing eye requiring repeated PDT treatments, would cost a third party payer around £31 607 per QALY. Model 2, assuming a baseline VA of 6/60 and predominantly classic CNV in the better seeing eye requiring repeated PDT treatments, would cost around £63 214 per QALY. Although there are no absolute standards for cost effectiveness, Canadian (and de facto American) guidelines proposed by Lauapitis et al put the model 1 outcome into the moderate cost effectiveness category and the model 2 outcome close to the cost ineffective category.

By comparison, the Sharma (US) 2 model found a cost per QALY of £56 716 and the Meads (UK) 1 year model found a cost per QALY of £137 138 excluding the savings from reduced levels of vision impairment (table 5). Our models differ from the other published models in three key areas.

(1) We assumed that the difference in visual acuity between treatment and placebo groups can be maintained over the affected individuals’ expected lifespan by continuing PDT treatments where necessary. The TAP extension data

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Table 2: Unit costs for photodynamic therapy with verteporfin using Australian Medicare Benefits Schedule (MBS) item numbers

<table>
<thead>
<tr>
<th>Photodynamic therapy</th>
<th>Unit cost</th>
<th>£</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial consultation</td>
<td>MBS 104</td>
<td>69</td>
</tr>
<tr>
<td>Fluorescein angiogram</td>
<td>MBS 11212 and 11215</td>
<td>166</td>
</tr>
<tr>
<td>Verteporfin, 1.5 mg vial</td>
<td>Federal Health budget</td>
<td>2100</td>
</tr>
<tr>
<td>Subsequent consultations</td>
<td>MBS 42884</td>
<td>360</td>
</tr>
<tr>
<td>Total for 1 treatment</td>
<td>MBS 105</td>
<td>35</td>
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<td></td>
<td></td>
<td>2670</td>
</tr>
</tbody>
</table>

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Table 3: Expected value for photodynamic therapy (PDT) with verteporfin versus placebo treatment in those with initial visual acuity of 6/12

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Probability</th>
<th>Utility</th>
<th>Result</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable visual acuity</td>
<td>0.591</td>
<td>0.81</td>
<td>0.479</td>
<td>0.712</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>0.409</td>
<td>0.57</td>
<td>0.233</td>
<td></td>
</tr>
<tr>
<td>Placebo treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable visual acuity</td>
<td>0.313</td>
<td>0.81</td>
<td>0.254</td>
<td>0.645</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>0.687</td>
<td>0.57</td>
<td>0.392</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>0.067</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% difference</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
covering 3 year follow up provide support for this assumption.

(2) We adjusted our mortality rates for the increased mortality associated with visual impairment an AMD, thereby producing a 7 year model.

(3) We did not include any disutility associated with PDT treatment, unlike the Sharma models.

Modelling over a longer time frame does affect the results found. This occurs because the treatment is expensive and the largest costs occur upfront, whereas the benefits occur when visual acuity fails to deteriorate in the future. By only modelling over 1 or 2 years, any benefit (utility or QALY) occurring thereafter is ignored; however, all the associated costs have already been incurred and thus are tallied against the existing, smaller, benefit. In effect by doing so, the modeller is making an implicit assumption that there is no future benefit from the treatment. We now know this is not the case. Sharma et al. did produce 11 year cost utility models for PDT but discounted the findings because of the lack of supporting data at that time.

Our study also does not take into account a number of the potential benefits from a reduction in reported impacts on independent living from vision impairment in an older population, as found in various population based studies of eye disease. The Blue Mountains Eye study has reported that corrected visual acuity worse than 6/18 is associated with an eightfold increased risk of hip fracture and a 27% attributable risk for hip fracture from vision impairment. Vision impairment of 6/12 and worse is associated with a threefold increase in the use of health and community care services (for example, meals on wheels, home help), a 1.8-fold increase in admissions to nursing homes, together with impaired self rated health and health related quality of life.

A recent TAP report demonstrated that verteporfin therapy reduced the risk of a clinically relevant loss of vision by 21% at 1 year, 16% at 3 years, and 7% at 5 years. The results of our study are consistent with these findings and suggest that verteporfin therapy may be cost effective for the treatment of neovascular AMD.

Table 4  Expected value for photodynamic therapy (PDT) with verteporfin versus placebo treatment in those with initial visual acuity of 6/60

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Probability</th>
<th>Utility</th>
<th>Outcome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable visual acuity</td>
<td>0.591</td>
<td>0.52</td>
<td>0.307</td>
<td>0.471</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>0.409</td>
<td>0.4</td>
<td>0.164</td>
<td></td>
</tr>
<tr>
<td>Placebo treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable visual acuity</td>
<td>0.313</td>
<td>0.52</td>
<td>0.163</td>
<td>0.438</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>0.687</td>
<td>0.4</td>
<td>0.275</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>0.033</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% difference</td>
<td>7.6%</td>
<td></td>
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</tbody>
</table>

$^*$Photodynamic therapy
$^\dagger$Quality adjusted life years

Figure 1  Model 1: one way sensitivity analysis of incremental cost effectiveness ratios (cost per QALY) for each scenario.

Figure 2  Model 2: one way sensitivity analysis of incremental cost effectiveness ratios (cost per QALY) for each scenario.
contrast sensitivity, with the greatest effect in patients with predominantly classic subfoveal CNV. This could be due to the development of a flatter and smaller scar in treated patients. Given the association between contrast sensitivity and visual disability and its importance as a predictor of falls, and possibly, hip fractures, the beneficial effects of verteporfin therapy on contrast sensitivity outcomes are likely to also have a favourable impact on patients’ daily activities. Economic modelling is only as good as the underlying data used. The TAP study is a well conducted, randomised controlled study and can be regarded as level 2 data. The utility assessment has been used in the other cost utility studies and has been peer reviewed. The unit cost data were taken from an Australian setting. The converted PDT cost figure, however, is comparable to published UK figures. The sensitivity analysis gives a range of effects that enable robust cost generalisation across similar populations of European origin.

It must be borne in mind that model 1 is close to being a best case scenario as far as assessing the cost utility of PDT is concerned, as it assumes reasonable vision in the affected and better seeing eye. As ophthalmic utilities are a function of vision in the better seeing eye, if the CNV affected eye was partnered by another good seeing eye, the changes in utility after treatment would be smaller (and hence the treatment less cost effective). The model 2 data are relevant, as funding is available in many countries for patients with initial visual acuity reduced to 6/60. Our analysis indicates a reduced cost utility for this level of initial visual function. Finally, in those with poor initial visual acuity, at around £63 214 per QALY, our estimates may be pessimistic because of assumptions made regarding the need for continuing treatment. Our findings have relevance for health policy decision makers.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Comparison of cost utility output from different published modelling approaches with different visual acuity (VA) starting points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model</strong></td>
<td><strong>Details</strong></td>
</tr>
<tr>
<td>Hopley et al (this study)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Reasonable VA, continuous PDT, 7 year model</td>
</tr>
<tr>
<td>Model 2</td>
<td>Poor VA, continuous PDT, 7 year model</td>
</tr>
<tr>
<td>Sharma et al</td>
<td></td>
</tr>
<tr>
<td>Base case 1</td>
<td>Reasonable VA, 2 years PDT, 2 year model</td>
</tr>
<tr>
<td>Base case 2</td>
<td>Poor VA, 2 years PDT, 2 year model</td>
</tr>
<tr>
<td>Meads et al</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1 year model</td>
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</tbody>
</table>

**REFERENCES**


**CONCLUSIONS**

AMD is a major problem affecting many older people in the developed world. Preventive measures can be taken for early AMD (smoking cessation and use of zinc/antioxidant supplements). PDT is at least moderately cost effective, at around £31 607 per QALY, in people with reasonable visual acuity given our assumptions (for example, better eye affected, reasonable initial visual acuity, predominantly classic CNV lesion). PDT, however, is relatively cost ineffective in those with poor initial visual acuity, at around £63 214 per QALY. Our estimates may be pessimistic because of assumptions made regarding the need for continuing treatment. Our findings have relevance for health policy decision makers.

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