Computerized Model of Cost-Utility Analysis for Treatment of Age-Related Macular Degeneration

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Purpose: To present a computerized model assessing individualized cost utility for current treatments for neovascular age-related macular degeneration (AMD) to enhance discussion regarding treatment options.

Design: Case- and eye-specific cost-utility analysis using individual case scenarios.

Participants: Visual acuity data from published randomized controlled trials are incorporated into this analysis.

Methods: Computerized model (Microsoft Visual Basic 6.0 programming) to establish preference-based cost-utility analysis in association with individual cost of treatment and blindness for neovascular AMD for both the better and worst seeing eye, with extrapolation of results over a 5-year term.

Main Outcome Measures: Cost per quality-adjusted life-year (QALY) and cost per QALY gained for comparison of treatments for specific visual acuities.

Results: All treatments show an increase in utility in comparison with best supportive care (BSC) if the better-seeing eye is treated. Ranibizumab, using the Phase IIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularisation (CNV) with or without Classic CNV Secondary to AMD (PIER) regimen, is the most cost effective at $626 938 per QALY gained for treatment of the better seeing eye. To increase utility value when treating the worst seeing eye, the vision must improve to such a degree that it becomes the better seeing eye. This level of improvement is only possible if there is <9 letters difference between the 2 eyes and treated with ranibizumab. Over 5 years, increasing influence from the cost of blindness results in increasing costs for those treatments unable to stabilize vision. Within 5 years, the cost per QALY for the BSC is greater than all treatments except monthly ranibizumab injections.

Conclusions: Assessment of cost of treatment incorporates both effectiveness of treatment, cost of treatment, and cost of blindness. Cost analysis enables incorporation of these aspects of treatment with the quality of life data to provide a better comparison of treatments over time. This analysis has provided a method for individual analysis and therefore can provide the structure for resource allocation.

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Age-related macular degeneration (AMD) is the leading cause of blindness in the Western world. With an increasing aged population, this carries with it an associated burden of disease from AMD with important public health considerations. The level of visual impairment can have significant impact on quality of life, which may result in increased use of health care resources. Patients with AMD have higher reported incidences of depression, anxiety, and falls, and require increased input from social support networks.

Recent advances in AMD treatment have provided diverse treatment options providing stability and in some cases improvement of vision. Wide-ranging efficacy and costs, however, produce an increasing need for economic evaluation alongside that of therapeutic efficacy. Cost-utility analyses of each treatment incorporates quality-of-life analyses, which provide valuable information when considering resource allocation by bridging the gap between objective and subjective outcome measures and the cost of providing such treatments.

Previous ophthalmic cost utilities have mostly assumed analysis based on the better seeing eye with only recent publications looking at ranibizumab with both the 1st and 2nd eyes and mixed scenarios. For this analysis, we provide an overview of the cost-utility associated with AMD treatments incorporating actual visual acuities from both eyes, with an output, which includes the quality-adjusted life-year (QALY) for all treatments for direct comparison. This is embodied in a computer model for ease of use. (Software is available from the authors upon request).

Methods

To perform cost-utility analyses, several aspects of treatment need to be considered. The “gain” seen from a treatment can be mea-
sured by the therapeutic efficacy, measured as visual outcome in this analysis and also in improvement in quality of life, measured in utilities.

The cost of the treatment is compared with the cost of no active treatment (i.e., best supportive care [BSC]). It is not only dependent on the direct cost of the individual drug, but the treatment regimen. Cost of blindness is included, once the outcome vision falls below legal blindness. This analysis is from a payer’s perspective.

Utility

Utilities provide a patient perceived value of a treatment and so defines the quality of life in association with a particular health state. They encompass not only the functional ability and health, but also their socioeconomic status and support systems. Their unit of measure is the QALY. A utility value of 1 is perfect health and 0 is death. There are several different methods of producing a preference based utility value; however, time trade-off methodology provides reliable and reproducible utility values for a specific level of vision\(^\text{†}\) and therefore is used in this analysis. It correlates closely with the vision in the better seeing eye\(^3\) rather than the one undergoing treatment. The utilities seem to be independent of pathology, time, and race. Time trade-off has been evaluated specifically for AMD and was therefore used in this analysis.

The utility \((U)\) for each visual acuity \((x)\) can be calculated using the formula from Sharma’s work:\(^4\):

\[
U_x = (0.374 \times \text{Snellen visual acuity}) + 0.514
\]

This calculation uses Snellen visual acuity. Published trial data for all AMD treatments uses Early Treatment of Diabetic Retinopathy Study (ETDRS) charts. By correlating the ETDRS number of letters to the decimal fraction of Snellen, an empirical function was derived such that a continuous conversion of visual acuities could be attained in the computer program.

Snellen visual acuity\(^7\) = 0.0199 \times \text{EXP}(0.461 \times \text{ETDRS letters read})

where \(^7\) is a decimal conversion. This allows calculation of exact utility from the ETDRS letters.

Therapeutic Efficacy

The visual acuity data used in this study were obtained from published trial data, thus providing a probability of a visual outcome after treatment (Table 1).

The utility value is assigned to each visual outcome with the aid of a decision tree (Fig 1). This has 4 policy branches, one for each of the treatments. For each treatment arm, the probability of each visual outcome is calculated based on the current trial data for that specific treatment; for example, the probability of a 15-letter improvement as detailed in the Phase III Study of Ranibizumab for Neovascular Age-Related Macular Degeneration Trial (MARINA\(^9\); Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) is 33%. The probability of each potential visual outcome is calculated and then multiplied by the utility for that vision. The sum of these utility values represents the treatment utility:

\[
\text{Treatment utility } (U_{Rx}) = \sum[U_x \times \text{probability of visual outcome } (p)]
\]

The utilities assume this calculation on the vision in the better seeing eye. The probability of a change in vision is calculated and if this outcome is above that of the fellow eye, then the utility for that eye is used. If it is below that of the fellow eye, then the utility for the fellow eye is used. This allows calculation on both a first and second eye basis, allowing for a more practical analysis. It is assumed in the decision tree that the probability of each visual outcome remains the same, irrespective of the baseline vision and the number of treatments required.

Disutility

The disutility of a treatment is associated with complication rates or adverse events. Disutilities resulting from adverse visual events are reflected in the visual outcome and, therefore, are already included in the calculation. Disutility values for nonocular adverse events such as thromboembolic events and hypertension have been established in several studies\(^1,12\); however these adverse events were not seen to be significantly different than in the sham group during the MARINA or VEGF Inhibition Study in Ocular Neovascularisation (VISION)\(^8\) trials and therefore would have no significant impact across all groups. With this in mind, the overall disutility associated with adverse events such as photodynamic therapy have also been assessed by assigning utilities from a discussion forum rather than direct measurement.\(^13\) This analysis included both of the above disutility measurements in their respective treatment groups.

The average age of the AMD patient is assumed to be longer than the duration of this cost-effectiveness analysis. Cost effectiveness is only seen if there is a change in utility. As such, because utility is dependent on the vision in the better seeing eye, when treating the first eye, to see a change in utility the vision in the treatment eye would have to improve to above the level seen in the better seeing eye. The change in utility is calculated by

<table>
<thead>
<tr>
<th>Vision</th>
<th>BSC(^7)</th>
<th>PDT(^7)</th>
<th>Pegaptanib(^8)</th>
<th>Ranibizumab(^9)</th>
<th>Ranibizumab(^10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6 lines improved</td>
<td>0</td>
<td>0.01</td>
<td>0.1</td>
<td>0.33</td>
<td>0.13</td>
</tr>
<tr>
<td>≥3 lines to &lt;6 lines improved</td>
<td>0.038</td>
<td>0.08</td>
<td>0.12</td>
<td>0.57</td>
<td>0.38</td>
</tr>
<tr>
<td>≥1 lines to &lt;3 lines improved</td>
<td>0.062</td>
<td>0.065</td>
<td>0.13</td>
<td>0.24</td>
<td>0.39</td>
</tr>
<tr>
<td>No change in visual acuity</td>
<td>0.126</td>
<td>0.147</td>
<td>0.31</td>
<td>0.075</td>
<td>0.1</td>
</tr>
<tr>
<td>≥1 lines to &lt;3 lines decreased</td>
<td>0.15</td>
<td>0.229</td>
<td>0.31</td>
<td>0.075</td>
<td>0.1</td>
</tr>
<tr>
<td>≥3 lines to &lt;6 lines decreased</td>
<td>0.324</td>
<td>0.289</td>
<td>0.31</td>
<td>0.075</td>
<td>0.1</td>
</tr>
<tr>
<td>≥6 lines decreased</td>
<td>0.3</td>
<td>0.182</td>
<td>0.1</td>
<td>0.025</td>
<td>0.1</td>
</tr>
</tbody>
</table>

BSC = best supportive care; PDT = photodynamic therapy.

\(^1\)One-year data only from Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab (PIER).
comparing it with the utility associated with BSC, that is, QALYS gained with that treatment:

\[
\text{QALYS gained} = \frac{U_{RX}}{U_{BSC}}
\]

Cost of Treatment

Patient Population. A 2-year cost-effectiveness model has been created using published trial data. Our model assumes a similar cohort of patients.

Relevant Costs. We have included variable incremental costs over 2 years in our calculation. Fixed costs, such as administration and capital expenditures, have not been included because they were thought to be approximately equivalent in all arms. A discount rate of 3% was employed to these costs. Costs of investigation and treatment were based on the Current Procedural Terminology (American Medical Association; Table 2).

The BSC incurs initial consultation and investigations costs (including baseline optical coherence tomography and fundus fluorescein angiography) with quarterly follow-up costing $689 over 2 years. The cost utility ratio is then calculated using the cost of the treatment in comparison with the BSC:

\[
\text{Cost utility ratio} = \frac{\text{Cost of treatment}}{\text{Cost of BSC}}
\]

Table 2. Costs of Investigation and Treatment

<table>
<thead>
<tr>
<th>Costed Item</th>
<th>Unit Cost (USD)</th>
<th>1st Year</th>
<th>2nd Year</th>
<th>Cost (USD) (2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDT (includes IV infusion)</td>
<td>331.69</td>
<td>3.4</td>
<td>2.2</td>
<td>10,542</td>
</tr>
<tr>
<td>Pegaptanib</td>
<td>995</td>
<td>8.4</td>
<td>6.9</td>
<td>20,139</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>1950</td>
<td>12</td>
<td>12</td>
<td>53,876</td>
</tr>
<tr>
<td>Ranibizumab†</td>
<td>1950</td>
<td>6</td>
<td>4</td>
<td>22,744</td>
</tr>
<tr>
<td>Initial visit</td>
<td>176.88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up visit</td>
<td>53.96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmoscopy</td>
<td>23.54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>135.59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optical coherence tomography</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verteporfin</td>
<td>1288</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravitreal injection</td>
<td>185</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Owing to the variation in uptake, a high and low estimation can be calculated and used in a sensitivity analysis of cost per QALY gained. Sensitivity analysis of costs is incorporated within the proportionality of the calculation.

QALYS Gained

Cost of Blindness. In addition to the cost incurred by the treatment, the cost of blindness is incorporated once the vision falls below 35 letters. The cost of blindness varies by geographic location; the proportion of cost incurred for people with AMD is detailed below (Table 3). The cost of blindness measurements do not take into account any personal expenditure or loss of earnings.

Figure 1. Decision tree: Method for assigning visual change according to trial data. AMD = age-related macular degeneration; BSC = best supportive care; PDT = photodynamic therapy.
Incremental Cost Effectiveness Ratio

The cost-effective values describe whether an intervention is cost effective. This level varies based on the current climate. It is generally thought that if you gain $50,000 per QALY, then that intervention is cost effective.\textsuperscript{15}

Results

To demonstrate the usefulness of this methodology, we examine 4 distinct scenarios. Although the absolute value for the cost per QALY data varies, its proportion in comparison with other treatments does not. Cost per QALY data, however, only provides information on the unit cost of the treatment regimen. It does not give any details regarding the effectiveness of the treatment.\textsuperscript{19}

Cost-effectiveness data, however, are measured in cost per QALY gained. This is the comparison of cost of all treatments to BSC with incorporation of the effectiveness of the treatment. Thus, there is no data for BSC in this area.

Scenario 1: Visual Acuity—Treated Eye, 53; Fellow Eye, 0

Figure 3 shows that, in treating the better eye, there is a benefit with all treatments in comparison with BSC. Ranibizumab using the Ranibizumab, using the Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization (CNV) with or without Classic CNV Secondary to AMD (PIER) regimen is the most cost-effective proven treatment; this holds true for all values whereby the better eye is treated. This scenario is common place because of the nature of AMD, where there is a high risk of both eyes being affected.

Scenario 2: Visual Acuity—Treated Eye, 42; Fellow Eye, 35

In the case where the visual acuities are similar in both eyes and close to the level of blindness, an increasing proportion of cost is due to the cost of blindness. Ranibizumab is the only cost-effective

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### Table 3. Cost of Blindness

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estimated Cost (GBP)</th>
<th>Proportion of Uptake (%)</th>
<th>GBP</th>
<th>USD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blind registration (one off)</td>
<td>59.70±37.71</td>
<td>94.5</td>
<td>92.05</td>
<td>146.81</td>
</tr>
<tr>
<td>Low vision assessment</td>
<td>136.33</td>
<td>33</td>
<td>44.99</td>
<td>71.75</td>
</tr>
<tr>
<td>Low vision rehabilitation</td>
<td>205.30</td>
<td>11</td>
<td>22.58</td>
<td>36.01</td>
</tr>
<tr>
<td>Housing benefit and council tax benefit</td>
<td>2714.40</td>
<td>45</td>
<td>1221.48</td>
<td>1948.13</td>
</tr>
<tr>
<td>Social security</td>
<td>1,924</td>
<td>63</td>
<td>1212.12</td>
<td>1933.21</td>
</tr>
<tr>
<td>Tax allowance</td>
<td>319</td>
<td>5</td>
<td>16</td>
<td>25.52</td>
</tr>
<tr>
<td>Depression</td>
<td>391.97</td>
<td>38.6</td>
<td>151.3</td>
<td>241.30</td>
</tr>
<tr>
<td>Hip replacement</td>
<td>3669</td>
<td>5</td>
<td>188.45</td>
<td>292.58</td>
</tr>
<tr>
<td>Community care</td>
<td>2848.63</td>
<td>6</td>
<td>170.92</td>
<td>272.60</td>
</tr>
<tr>
<td>Residential care</td>
<td>15 904.41 (with 30% discount)</td>
<td>30</td>
<td>3339.93</td>
<td>5326.84</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>10 295</td>
<td></td>
</tr>
</tbody>
</table>

GBP = Great Britain pound; USD = United States dollar.\textsuperscript{18} Conversion to USD using purchasing power parity.

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**Figure 2.** Cost per QALY with the visual acuity in the treated eye at 53 letters and no letters read in the fellow eye. QALY = quality-adjusted life-years; USD = United States dollar.\textsuperscript{19} Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to AMD (PIER) regimen.

**Figure 3.** Cost per QALY gained with the visual acuity in the treated eye at 53 letters and no letters read in the fellow eye. QALY = quality-adjusted life-years; USD = United States dollar.\textsuperscript{19} Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to AMD (PIER) regimen.
treatment in this situation; this form of treatment is able on average to stabilize vision and hence negate the cost of blindness. In this situation, when treating the better seeing eye, only those treatments that are able to prevent a decrease in vision are cost effective.

Scenario 3: Visual Acuity—Treated Eye, 35; Fellow Eye, 53
In this case, none of the treatments are able to improve the vision in the treatment eye above that of the fellow eye. No gain in QALY is seen and therefore none of the treatments are cost effective.

Scenario 4: Visual Acuity—Treated Eye, 51; Fellow Eye, 53
If visual acuities are similar in both eyes and the worst seeing eye is treated, then only those treatments that are able to improve vision to such a degree to produce a change in utility become the most cost effective. This effect is seen in up to 9 letters difference between the 2 eyes, beyond which no treatment is cost effective. Ranibizumab is again the only cost-effective treatment in this case.

Scenario 5: Visual Acuity—Treated Eye, 53; Fellow Eye, 0
An additional treatment option includes the use of bevacizumab. If you assume a similar visual acuity outcome as based on current knowledge of response (only 1 year data and not as a result of a standardized randomised control trial) and a 2% risk of thromboembolic adverse event, and a cost of $50 per treatment then this would become the most cost effective in all cases (Fig 4). This model, however, only includes the disutility associated with thromboembolic events and not the full costs of treatment of these adverse events. It is hoped that once results from the Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (CATT) become available, then this portion of the model can be updated accordingly.

These results are, however, over a short-term basis. We only have long-term vision data on the photodynamic therapy and pegaptanib studies; however, once further results on the other treatments become available, then these analyses can be refined accordingly. It is thought that the gradual drop in vision over a 2-year period is not brought out in this study; therefore, the 5-year prediction can give us a better overview of the treatments that are most likely to be of benefit (Fig 5). These data are based on treatment of the better seeing eye with starting visual acuity of 53 letters.

Over a period of 5 years, the cost per QALY reduces as the number of treatments reduce and the vision stabilizes. This is in comparison with the BSC, where there is an increasing proportion of blindness and hence increasing costs. The cost per QALY for all treatments decrease over a 5-year period, in contrast with, BSC which shows an increase over the same time period. Within 5 years, the cost per QALY for the BSC is greater than all treatments except monthly ranibizumab injections.

If the cost of blindness is increased, for instance up to $20,000, then the cost per QALY for BSC at the end of 5 years is equal to that of ranibizumab provided on a monthly basis.

Discussion

Cost-effectiveness analysis allows calculation of cost per QALY gained, providing a mechanism for comparison across health care provisions. Inclusion of therapeutic effect, adverse events, and cost of treatment associated with a patient’s perceived benefit provides a more rounded analysis than costing alone. The utility associated with vision is related to the visual acuity in the better seeing eye. Treatments that are able to provide better end vision in comparison with BSC show an increase in utility and are therefore cost effective. In this analysis, we are able to provide a comparative cost analysis, which shows that despite ranibizumab having the highest unit cost; it is the most cost-effective treatment in most cases. In consideration for treatment of the first eye, it is the only treatment that on average
is able to improve vision and therefore is the only cost-effective treatment up to 9 letters difference between the 2 eyes. Cost-effectiveness analysis on ranibizumab confirms significant value above other treatments. This analysis does not include bevacizumab because only short-term data are available for visual acuity and adverse events; the assumption is that bevacizumab is equally therapeutically effective, and its cost effectiveness would be significantly better than all treatments owing to its low unit cost.

Treatment of the worst seeing eye is a controversial area during cost analysis. Disorders known to affect both eyes, although separated in severity and time, can result in severe visual loss if the first eye is not treated and the second eye shows either more aggressive features or poor response to treatment. This element is not taken into account in these analytical approaches.

Using 5-year data is a more realistic method for input into resource allocation and this can be adjusted once substantiated data points are available. Ranibizumab is able to stabilize or improve a higher proportion of patients, thus reducing the influence from the cost of blindness.

These analyses rely on several measures. Data regarding the therapeutic effect is gained from clinical trials. Increasingly, trials for AMD include different measures of therapeutic effect in addition to visual acuity such as contrast sensitivity and reading speed. These differing measurements may represent a more functional therapeutic effect and thus correlate more closely with health-related quality-of-life measurements.

A limitation of this study is that the therapeutic data for the different treatment regimens involved comparable but different populations. Assumptions are made that the groups have a similar entry criteria with the knowledge that the early studies may have had an overrepresentation of patients with advanced AMD. This would affect the visual outcomes; therefore, trials with direct comparisons would provide more suitable data.

The second measures include the QALY assessment. The QALY assessments have been shown to be reliable and reproducible. In patients with AMD, however, the time trade-off utility value has been shown to be lower in patients who have had visual loss for <1 year versus those who have had it for >1 year. This indicates an improvement in the quality of life of people with AMD with time, probably owing to adjustment to using peripheral vision and maintenance of independence after a sudden decline in vision. Trials that assess the utility during the trial, that is, at the beginning and end of the trial, rather than a stand-alone correlation of utility with vision may be more accurate.

A further influence in the cost of these treatments is the cost of blindness. There are few data on the actual cost of blindness related to macular degeneration. The variety of costs incurred is wide-ranging and there is a variable uptake in resource requirements. This can lead to a gross underestimation in the actual cost, which has a significant effect on the estimation of cost per QALY gained, resulting in more significant cost implications in comparison with BSC.

Over a period of 5 years, although the BSC has the lowest unit cost, in time this has the highest proportion of blindness, which results in increasing overall incremental cost effectiveness. To a lesser degree, this element is seen in those treatments that are unable to stabilize vision. In cases where the vision falls to 35 letters, there is increasing effect from the cost of blindness; therefore, those treatments with a higher proportion of significant visual loss are affected by this element in the costing analysis, especially over a 5-year period.

Using this tool provides the ability to input individual patient data to calculate the most cost-effective treatment for the individual situation. This may have some input in helping to adjust resources allocation specific to your environment.

References


Footnotes and Financial Disclosures

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Footnotes:
1 King’s College Hospital, London, United Kingdom.
2 Kidde PLC, Colnbrook, Berkshire, United Kingdom.


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