The cost-utility of photodynamic therapy in eyes with neovascular macular degeneration: a value-based reappraisal with 5-year data


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined photodynamic therapy (PDT) using verteporfin, a photosensitising dye stimulated by illumination with a diode laser source emitting at a wavelength of 689 nm. PDT was used for the treatment of classic, subfoveal choroidal neovascularisation (CNV) associated with age-related macular degeneration (ARMD).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with classic CNV measuring 5,400 micrometres or less in greatest diameter, and associated with a best corrected visual acuity of 20/40 to 20/200.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1976 and 2005. The costs were estimated from 2004 sources. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.

Outcomes assessed in the review
The outcomes estimated from the literature were:

visual acuity estimates and corresponding utility values;

disutility values for adverse events (infection site adverse events, infusion-related back pain, allergic reactions and photosensitivity reactions);

the number of verteporfin treatment; and

life expectancy for a typical patient enrolled in the TAP study.
**Study designs and other criteria for inclusion in the review**

The primary studies appear to have been identified selectively rather than being obtained from a systematic review of the literature. Most utility values came from the TAP study, a randomised clinical trial enrolling 159 patients in the PDT group and 83 patients in the control group, with patients followed for 5 years. After 2 years, the study was carried on as an open-label extension, and only 77 patients of the initial 159 patients were still in the PDT group at 5 years. The analysis used logMAR data (log of the minimum angle of resolution) visual acuity, an instrument correlated with patient-based preferences. The utility data associated with adverse events were derived from a database of over 30,000 patient-based utility values. The time trade-off approach was used for both series of data. Life expectancy was estimated from National Vital Statistics.

**Sources searched to identify primary studies**

Not relevant.

**Criteria used to ensure the validity of primary studies**

The use of both a clinical trial and a large database enhances the validity of the primary studies.

**Methods used to judge relevance and validity, and for extracting data**

Not stated.

**Number of primary studies included**

Eighteen primary studies provided clinical data.

**Methods of combining primary studies**

Not relevant since each study provided a series of estimates.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

The mean visual acuity data (with corresponding utility values) were:

- 20/100 to 20/160+2 (utility 0.661) in the intervention group and 20/100 to 20/200-1 (utility 0.630) in the control group in the first year;
- 20/160+2 (utility 0.658) and 20/200-1 (utility 0.619) between the first and second years;
- 20/160 (utility 0.648) and 20/250+1 (utility 0.612) between the second and third years;
- 20/160 (utility 0.648) and 20/250 (utility 0.610) between the third and fourth years; and
- 20/160 (utility 0.648) and 20/250-2 (utility 0.604) between the fourth and fifth years.

Visual disturbance, retinal capillary non-perfusion and vitreous haemorrhage were already included with the TAP-study data. Thus, they were not included in the calculation of disutility values associated with adverse events.

In terms of adverse events:

- Injection site adverse events occurred in 13.4% patients in the intervention group and 3.4% in the placebo group;
infusion-related back pain occurred in 2.2% patients in the intervention group versus 0% in the placebo group; allergic reactions occurred in 1.2% patients in the intervention group versus 2.4% in the control group; and photosensitivity occurred in 12% of patients in the intervention group versus 0% in the control group.

The total disutility value associated with the frequency of these adverse events for the PDT group compared with the control group was 0.002.

The number of verteporfin treatments given to every patient was 3.5 in the first year, 2.3 in the second year, 1.1 in the third year, 0.4 in the fourth year and 0.1 in the fifth year.

The average life expectancy of patients enrolled in the TAP study was 12 years.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions to extend 5-year clinical trial data to a 12-year time horizon.

**Estimates of effectiveness and key assumptions**
From year 6 through year 12, 0.1 verteporfin treatments was given each year. Mean visual acuity data were 20/160+2 (utility 0.658) in the intervention group and 20/320+2 (utility 0.601) in the control group between year 5 and year 12. The duration of the verteporfin treatment benefit lasted until death.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the expected number of quality-adjusted life-years (QALYs). These were estimated by combining survival data and utility values that were derived from the literature. Since there was no change in length of life with PDT treatment, the QALY estimate was derived entirely from the improvement in quality of life. The QALYs were reported as either undiscounted or discounted (at 3% and 5% annual rates).

**Direct costs**
The analysis of the costs was carried out from the perspective of the third-party payer. It included the costs associated with intravenous fluorescein angiography, verteporfin, office visit, and physician PDT treatment fee. Only the extra costs associated with PDT treatment were considered. The unit costs were presented separately from the quantities of resources used for some cost items. Some resource use data were estimated from the TAP study. Some assumptions were also made. The costs were obtained from average national Medicare reimbursement rates (including associated co-payments). Discounting was relevant given the time horizon of the analysis, and two annual discount rates (3% and 5%) were applied. Undiscounted results were also reported. The price year was 2004.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not taken into consideration.

**Currency**
US dollars ($).

**Sensitivity analysis**
One- and two-way sensitivity analyses were carried out to address the issue of robustness of cost-utility ratios to variations in baseline clinical and economic data, such as costs, efficacy and frequency of treatment, utility values and age of the patient population. Alternative values and ranges were derived from the literature (i.e. confidence intervals for utility values) or were set by the authors (i.e. increases or reductions in costs). All sensitivity analyses were performed on costs and benefits discounted at an annual rate of 3%.

**Estimated benefits used in the economic analysis**
Over the 12-year time period, the undiscounted QALYs gained due to PDT over observation were 0.585 (0.4912 using a 3% annual discount rate; 0.4381 using a 5% annual discount rate).

Nine per cent of the total value was gained during the first 2 years, while 75% of the value was gained during the last 8 years.

**Cost results**
Over the 12-year time period, the total incremental and undiscounted costs associated with PDT over observation were $15,900 ($15,277 using a 3% annual discount rate; $14,915 using a 5% annual discount rate).

Ninety per cent of the costs were expended during the first 4 years of treatment, while 10% of the costs were expended during the last 8 years of treatment.

**Synthesis of costs and benefits**
An incremental cost-utility ratio was calculated to combine the costs and QALYs of PDT over observation. The incremental and undiscounted cost per QALY gained with PDT was $27,180 ($31,103 using a 3% annual discount rate; $34,407 using a 5% annual discount rate).

The sensitivity analysis showed that the greatest impact on the cost-utility ratio was that of substantial changes in treatment efficacy, with the incremental cost per QALY gained ranging from $20,736 (PDT efficacy increased by 50%) to $62,207 (PDT efficacy decreased by 50%). Variations in other data led to narrower ranges of cost-utility ratios, suggesting that the results of the analysis were quite robust.

**Authors’ conclusions**
The use of photodynamic therapy (PDT) for the treatment of age-related macular degeneration (ARMD) was a very cost-effective intervention in comparison with observation, with an incremental cost per quality-adjusted life-year (QALY) gained of $31,103.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. Observation was compared with PDT because this was the comparison that was carried out in the TAP study. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from published studies. A systematic review of the literature does not appear to have been undertaken to derive clinical estimates, and the primary studies were identified selectively. Most of the evidence came from a published clinical trial, which generally provided robust estimates. Extensive information on the design and other characteristics of the trial was given. The primary estimates were not combined and each study provided a series of estimates. Long-term inputs were based on authors’ opinions because trial-based data were limited to a 5-year time horizon. The use of sensitivity analyses to address the issue of uncertainty surrounding such estimates was helpful.
Validity of estimate of measure of benefit
The benefit measure used in the analysis was appropriate since QALYs capture the impact of the interventions on the most relevant dimensions of care (i.e. survival and quality of life). However, in this case, no survival advantage was associated with the treatment. Thus the benefit was entirely attributable to improvements in quality of life. A further advantage of QALYs is that they are comparable with the benefits of other health care interventions. Discounting was applied, as US guidelines for economic evaluations suggest, and the impact of using alternative discount rates or no discounting was investigated. Extensive information on the source of the utility weights was provided.

Validity of estimate of costs
The cost analysis, which focused on the direct medical costs, was consistent with the stated perspective. The unit costs and the quantities of resources used were presented separately for only some cost items. In general, the costs were expressed as macro-categories and a detailed breakdown of items (i.e. labour, materials, etc.) was not reported. This limits the possibility of replicating the cost analysis in other settings. The costs were treated deterministically in the base-case analysis, but variations in total costs were investigated in the sensitivity analysis. The source of the data was reported for all costs, whereas resource consumption was mainly derived from published data and authors’ assumptions. The price year was reported, which aids reflation exercises in other time periods.

Other issues
The authors reported the results of their previous cost-effectiveness analysis in narrative form, as well as the findings of other economic evaluations of PDT. The main differences between the current results and those from other studies were pointed out. In particular, in their previous study the current authors extrapolated long-term data using information from the first 2 years of the TAP study, while the availability of utility estimates from the first 5 years of the TAP study makes the current analysis more robust. However, the authors noted that the last 3 years of the TAP study were not blinded, which might have introduced some bias and confounding factors. The issue of the generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were carried out, which enhance in part the external validity of the analysis. The study referred to patients with ARMD and this was reflected in the authors’ conclusions.

Implications of the study
The study results suggested that PDT using verteporfin is a cost-effective treatment strategy for classic, subfoveal CNV associated with ARMD.

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