Cost-effectiveness and cost-utility analysis of travoprost versus latanoprost and timolol in the treatment of advanced glaucoma in five European countries: Austria, France, Germany, The Netherlands and the United Kingdom

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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
Three first-line treatments for advanced glaucoma were examined. These were travoprost 0.004% (TRA), latanoprost 0.005% (LAT) and timolol 0.05% (TIM). TRA and LAT were given once daily, while TIM was given twice daily.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with advanced glaucoma.

Setting
The setting was primary and secondary care. The economic study was carried out in five European countries, namely Austria, France, Germany, the Netherlands and the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2001. The resource use data for the UK were derived from an electronic database accessed in 2005. The resource use data for the other countries were based on expert opinion, thus dates were not reported. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A Markov model was constructed to simulate the clinical and economic outcomes associated with the three treatments in hypothetical patients with advanced glaucoma. After treatment, patients could experience stable or unstable visual acuity (VA) and two independent Markov states were specified. These states were stable glaucoma and visual field defect (VFD). Thus, patients were classified into either a stable glaucoma group or a new unstable VFD group. At the end of each cycle, patients could or could not develop a VFD. Patients who did not develop a VFD continued with current treatment, while those who did received a second-line treatment. The time horizon of the model was 5 years with cycles of one month (since glaucoma drugs are effective within 4 to 6 months). Simulations were performed over 60 cycles.
Outcomes assessed in the review
The outcomes estimated from the literature were the mean and variance of daily IOP, the probability of entering the model in the stable or unstable VA health states, and the utility weights of avoiding a VFD.

Study designs and other criteria for inclusion in the review
Most of the evidence came from a randomised clinical trial in which the three treatments were compared directly over 12 months in a sample of 596 patients with advanced glaucoma. This was the only clinical trial that carried out a direct comparison, and it was chosen as the primary source of effectiveness data. Few details on the other sources of data were reported.

Sources searched to identify primary studies
Not relevant.

Criteria used to ensure the validity of primary studies
The use of a clinical trial to derive the effectiveness of the three treatments was appropriate because this represents a robust source of data. The use of a direct comparison enhances the internal validity of the effectiveness results.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The clinical estimates were derived from three primary studies.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The analysis of the effectiveness showed that TRA was either equal to or superior to LAT, and superior to TIM.

The average daily IOP changed from 19.1 mmHg at week 2 to 19.6 mmHg at week 48 with TIM (all weeks together: 19.3), from 18.5 to 18.4 mmHg (18.3) with LAT, and from 17.7 to 18.2 mmHg (18.0) with TRA. The differences between TRA and TIM or LAT were statistically significant, (p<0.0001 and p<0.001, respectively).

The daily variance IOP changed from 4.58 mmHg at week 2 to 5.54 mmHg at week 48 with TIM (all weeks together: 4.82), from 3.70 to 4.00 mmHg (3.97) with LAT, and from 4.03 to 4.85 mmHg (4.22) with TRA. The differences between TRA and TIM was statistically significant, (p=0.04), while the difference between TRA and LAT did not reach statistical significance, (p=0.25).

The probabilities of entering the model in the stable and unstable VA health states were 77.8% and 22.2%, respectively.

The utility of avoiding a VFD was set at 0.04. This was obtained by applying a published formula.

Measure of benefits used in the economic analysis
The summary benefit measures used were the time without a VFD and quality-adjusted life-years (QALYs). The utility weights were obtained from published studies and from a survey of French patients. These data obtained were then used in a published formula from which the final estimates for the health states of the Markov model were estimated. Discounting was not carried out.

**Direct costs**
The analysis of the costs was carried out from the perspective of the payer. It included the costs associated with visits to ophthalmologists and general practitioners (GPs), clinical examinations, surgery, laser treatment and drugs. The unit costs and the quantities of resources used were presented separately for all items. In addition, monthly average costs were presented separately for the main categories of costs (drugs, visits, surgery, laser), for the health states of the model and for each country. French medical costs were derived from a cross-sectional, nationally-representative survey. British data were derived from a large database of patients in general practice, while drug costs came from the British National Formulary. Data for Austria, Germany and the Netherlands were obtained from a sample of 5 experts for each country with a deep knowledge of glaucoma management. The sources of the costs were clearly reported for all items and all countries. Discounting was relevant as the costs were incurred over a 5-year time horizon. The annual discount rate chosen in the analysis was 5%. The price year was 2003.

**Statistical analysis of costs**
The costs appear to have been treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not included.

**Currency**
Euros (EUR). The exchange rate from UK pounds sterling (£) to euros was 1 = EUR 1.5.

**Sensitivity analysis**
A probabilistic sensitivity analysis was carried out using Monte Carlo simulations. The robustness of the cost-utility ratios to variations in the probabilities for the stable and unstable VA health states to develop a new VFD, the loss of utility associated with a new VFD, and the costs of a stable and progressive patient, were assessed. The probabilistic distributions assigned to each model input were reported (normal and triangular distributions).

**Estimated benefits used in the economic analysis**
Time without a VFD was 3.417 years with TRA, 3.285 years with LAT and 2.812 years with TIM.

Expected QALYs over 5 years were 3.6210 with TRA, 3.6164 with LAT and 3.6001 with TIM.

**Cost results**
The total costs per patient over 5 years were:

- in Austria, EUR 1,612 with TRA, EUR 1,751 with LAT and EUR 859 with TIM;
- in France, EUR 1,225 with TRA, EUR 1,115 with LAT and EUR 855 with TIM;
- in Germany, EUR 1,886 with TRA, EUR 2,049 with LAT and EUR 1,229 with TIM;
- in the Netherlands, EUR 1,725 with TRA, EUR 1,821 with LAT and EUR 1,335 with TIM;
- in the UK, EUR 993 with TRA, EUR 1,041 with LAT and EUR 790 with TIM.
**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios and incremental cost-utility ratios were calculated in order to combine the costs and benefits of the alternative strategies.

In the comparison between TRA and LAT, TRA dominated LAT in all countries except France as TRA was both more effective (in terms of both time spent without VFD and QALYs) and less expensive. In France, the incremental cost per year without a new VFD was EUR 825 and the incremental cost per QALY gained was EUR 23,948.

In the comparison between TRA and TIM, the incremental cost per year without a new VFD was EUR 1,486 in Austria, EUR 1,109 in France, EUR 1,495 in Germany, EUR 923 in the Netherlands and EUR 823 in the UK. The incremental cost per QALY gained was EUR 43,053 in Austria, EUR 32,116 in France, EUR 43,296 in Germany, EUR 26,742 in the Netherlands and EUR 23,828 in the UK. Thus, considering a threshold for the cost-utility ratio of approximately EUR 33,000 to 50,000, TRA could be considered a cost-effective strategy in all countries.

The probabilistic simulation showed that the probability of an incremental cost per QALY being less than EUR 45,000 was always greater than 55% when comparing TRA and TIM, while it was much lower when comparing LAT and TIM. In comparison with TIM, it was always more likely that TRA would be more cost-effective than LAT. For example, in the UK, the probability of being cost-effective given the threshold of 45,000 EUR per QALY was 98.7% for TRA compared with TIM and 93.7% for LAT compared with TIM (highest probabilities). These values were, respectively, 72.2% and 27.5% in Germany and 58.7% and 15.9% (lowest probabilities) in France.

**Authors' conclusions**

Travoprost (TRA) was a cost-effective treatment for advanced glaucoma in comparison with timolol (TIM) or latanoprost (LAT) in Austria, France, Germany, the Netherlands and the UK.

**CRD COMMENTARY - Selection of comparators**

The authors justified their choice of the comparators, which represented commonly used treatments for the treatment of patients with advanced glaucoma. Details of doses and frequency of administration were provided. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

It appears that a systematic review of the literature was not performed to identify the primary studies. The authors stated that, at the time of the study, only one comparative trial was available, thus justifying the limited number of data sources. There was limited information on the design and characteristics of the other primary studies. However, the use, as the primary source of effectiveness data, of a randomised clinical trial that directly compared the three treatments under analysis and enrolled a large sample of patients should have ensured the internal validity of the study. The robustness of some clinical estimates was investigated in the probabilistic sensitivity analysis.

**Validity of estimate of measure of benefit**

Both a disease-specific and a generic benefit measure were used in the analysis. Both appear to have been appropriate in terms of assessing the impact of the interventions on the patients’ health. In particular, QALYs are useful not only because they assess the effect on quality of life, but also because they can be compared with the benefits of other health care interventions. Some information on the approach used to calculate the QALYs was reported. The authors stated that the same value of utility was used for all countries since this approach had already been used in other studies.

**Validity of estimate of costs**

The analysis of the costs was carried out in accordance with the perspective taken in the study. It was mainly based on published evidence (UK and France) and on the opinions of expert panels for countries in which national databases were not available (Germany, Austria, the Netherlands). Extensive details on the unit costs and quantities of resources
used were provided, which will enhance the possibility of replicating the analysis in other settings. No statistical analyses of the costs were performed and, with the exception of one estimate, the cost estimates were specific to the study setting. The impact of using alternative economic estimates was not investigated. The price year was reported, which will facilitate reflation exercises in other time periods. The authors acknowledged that the choice of the discount rate was arbitrary given the lack of agreement across the five countries.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. However, the use of a probabilistic sensitivity analysis increases the external validity. In addition, the study was performed in five different countries, thus implicitly addressing the issue of transferability between settings. The study referred to patients with advanced glaucoma and this was reflected in the authors’ conclusions. Side effects were not considered in the model given the similar safety profiles of the three drugs. The authors pointed out that the results of the current study were very conservative, thus larger differences between TRA and its comparators could be expected.

Implications of the study
The study results support the use of TRA as the treatment of choice for patients with advanced glaucoma. The authors pointed out that the current findings should be corroborated by prospective data in glaucoma patients.

Source of funding
Supported by Alcon Laboratories Inc., Fort Worth (TX), USA.

Bibliographic details

Other publications of related interest
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Indexing Status
Subject indexing assigned by CRD

MeSH
Austria; Cloprostenol /therapeutic use /economics; Cost-Benefit Analysis; Drug Therapy, Combination; France; Germany; Glaucoma /drug therapy /economics; Great Britain; Intraocular Pressure; Markov Chains; Netherlands; Prostaglandins F, Synthetic /therapeutic use /economics; Quality-Adjusted Life Years; Timolol /economics /therapeutic use; Treatment Outcome
AccessionNumber
22006007642

Date bibliographic record published
28/02/2007

Date abstract record published
28/02/2007