Prevention of herpes simplex virus eye disease: a cost-effectiveness analysis
Lairson D R, Begley C E, Reynolds T F, Wilhelmus K R

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 use of oral acyclovir (400 mg twice daily) for the prevention of ocular herpes simplex virus (HSV).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with a history of herpetic eye disease.

Setting
The setting was primary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness and resource use data were mainly derived from studies published in 1998 and 2000. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies, mainly based on a single trial (see Other Publications of Related Interest).

Modelling
A decision tree model was constructed to assess the costs and benefits associated with the three strategies under evaluation. The time horizon of the model was one year. The structure of the tree was depicted. The model was populated with data derived mainly from the literature.

Outcomes assessed in the review
The outcomes assessed were:

the reduction in the annual probability of recurrent HSV disease due to acyclovir over placebo,

the frequency of adverse events,

the annual probability of recurrent SK in patients who had a history of prior SK,
the proportion of patients undergoing corneal transplantation.

**Study designs and other criteria for inclusion in the review**
The evidence came from several publications of the same randomised, clinical trial. Thus, a review of the literature was not undertaken.

**Sources searched to identify primary studies**
Not relevant.

**Criteria used to ensure the validity of primary studies**
The validity of the primary study was ensured by the design of the trial.

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

**Number of primary studies included**
Two primary studies were used.

**Methods of combining primary studies**
Not stated.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The annual probability of recurrent HSV disease decreased by a relative risk reduction of 45%, from 32% among placebo-treated patients to 19% among acyclovir-treated patients.

Four per cent of patients discontinued treatment due to adverse events. Fifty per cent of adverse events were gastrointestinal and 10% were rashes. Other adverse events included dizziness, weight gain, headache, fatigue, sexual dysfunction, memory loss, anxiety, tinnitus and hair loss.

The annual probability of recurrent SK in patients who had a history of prior SK decreased by a relative risk of 43%, from 28% in placebo-treated patients to 14% in acyclovir-treated patients.

The proportion of patients undergoing corneal transplantation was 1.4%.

Given these data, the following probabilities were used in the decision tree:

- the probability of adverse events with acyclovir was 4%;
- the probability of infections was 32% for patients receiving no prophylaxis, 18% when acyclovir was given to all patients without adverse events, 25% when acyclovir was given to all patients and caused adverse events, and 23% when acyclovir was given to patients with a history of SK;
- the probability of SK was 48% in all branches;
- the probability of undergoing surgery was 2% for patients receiving no prophylaxis or when acyclovir was given to all patients.
patients, and 4% when acyclovir was given to patients with a history of SK.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the number of recurrent infections prevented during the 12-month period. It was derived from the decision model and no discounting was applied.

**Direct costs**
Discounting was not relevant since the costs were incurred during less than 2 years. The unit costs and the quantities of resources used were presented separately. The health services included in the economic analysis were drugs, physician visits and surgical procedures. The cost/resource boundary of the payer was adopted. Resource use was estimated mainly using prospectively collected data derived from patients in the trial. Some assumptions were also made. The costs were estimated from wholesale prices and Medicare payments. The costs were presented in 2001 values, using the medical care component of the Consumer Price Index, when necessary.

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

**Indirect Costs**
The indirect costs, such as time spent for transportation, waiting and examination, which were relevant to the patient, were included in the analysis. The unit costs were presented separately from the quantities of resources used. To estimate the time spent for transportation, distances were estimated using ZIP codes for clinics and patients. The time spent waiting for care and examination was derived from the Medical Expenditure Panel Survey. Average wages were used to assess the unit costs. Some resources, such as access to acyclovir care, treatment of recurrent infections, or surgical procedures, were based on authors’ assumptions. Discounting was not relevant and the price year was 2001.

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate sensitivity analyses were conducted to assess the robustness of the cost-effectiveness ratios. The variables investigated were the daily cost of acyclovir, the probability of infection, and the probability of surgery given the occurrence of SK. The ranges of values used were based on the observed lowest and highest estimates. Two-way sensitivity analyses were conducted for the probabilities of infection in the placebo and treatment groups. All sensitivity analyses were carried out under two main scenarios in which the indirect costs were either included or excluded.

**Estimated benefits used in the economic analysis**
The number of recurrent infections was 0.461 with no prophylaxis, 0.226 with acyclovir for all patients, and 0.272 with acyclovir for patients with prior SK. Thus, acyclovir for all patients prevented 0.325 recurrent infections relative to no prophylaxis, and 0.046 recurrent infections relative to acyclovir for patients with prior SK.

**Cost results**
The total costs were $299 with no prophylaxis, $2,304 with acyclovir for all patients, and $2,329 with acyclovir for patients with prior SK.

The extra costs were $2,005 with acyclovir for all patients over no prophylaxis, and $25 for acyclovir for patients with prior SK over acyclovir for all patients.
When the indirect costs were excluded, the estimated costs were $189 with no prophylaxis, $1,837 with acyclovir for all patients, and $1,852 with acyclovir for patients with prior SK.

The extra costs were $1,647 with acyclovir for all patients over no prophylaxis, and $15 for acyclovir for patients with prior SK over acyclovir for all patients.

**Synthesis of costs and benefits**
Average and incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the interventions under evaluation.

The average cost per recurrent infection prevented was $649 with no prophylaxis, $10,195 with acyclovir for all patients, and $8,549 with acyclovir for patients with prior SK.

The incremental analysis showed that the incremental cost per recurrence prevented with acyclovir for all patients over no prophylaxis was $8,532, while acyclovir for patients with prior SK was dominated by the strategy of acyclovir for all patients.

When the indirect costs were excluded, the average cost per recurrent infection prevented was $411 with no prophylaxis, $8,128 with acyclovir for all patients, and $6,800 with acyclovir for patients with prior SK.

As in the analysis of the direct costs, the incremental analysis showed that the incremental cost per recurrence prevented with acyclovir for all patients over no prophylaxis was $7,009, while acyclovir for patients with prior SK was dominated by the strategy of acyclovir for all patients.

The sensitivity analysis showed that when the estimates of probability of recurrence favoured acyclovir (very low for acyclovir-treated patients and very high for placebo-treated patients), the cost-effectiveness ratios decreased substantially (about $800 per recurrent infection prevented) making acyclovir very cost-effective over placebo.

**Authors’ conclusions**
Acyclovir treatment for the prevention of herpes simplex virus (HSV) eye disease was associated with a high cost per recurrence prevented in comparison with no prophylaxis. Similarly, the intervention was not cost-effective even among patients at higher risk of recurrences, such as those with a history of stromal keratitis (SK).

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator (no intervention) was appropriate, as the aim of the analysis was to assess the active value of acyclovir treatment. However, it was unclear whether no prophylaxis represents an actual strategy of care for patients with HSV. A strategy of limiting acyclovir to patients at higher risk of developing recurrences was appropriately considered. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The bulk of evidence on the efficacy of the intervention was derived from a couple of publications of a clinical trial. Therefore, a review of the literature was not undertaken. The design of the trial ensured the internal validity of the source used, although only few details on the study sample were provided.

**Validity of estimate of measure of benefit**
The summary benefit measure was specific to the intervention considered in the study and is therefore not comparable with the benefits of other health care interventions. It was obtained from the decision model, which represented disease progression. The impact of the intervention on the patients’ quality of life was not investigated.

**Validity of estimate of costs**
Two different perspectives were adopted in the economic evaluation. As such, all the costs relevant to both perspectives appear to have been included in the analysis. The cost analysis was conducted satisfactorily as the quantities of resources used and the unit costs were presented separately, which enhances the possibility of replicating the study. The source of the data was reported, as was the price year, which makes reflation exercises in other settings easy. The cost of treatment, the main cost driver, was varied in the sensitivity analysis. However, no statistical tests of the costs were carried out and the estimates were specific to the study setting. Further, some assumptions were made to assess some estimates, which were not varied in the sensitivity analysis.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. Few sensitivity analyses were conducted and the overall external validity of the analysis was low. Further, it appears that the sensitivity analysis investigated only those assumptions that favoured acyclovir, while worst-case scenarios were not considered. The authors noted some shortcoming of the analysis. First, the influence of HSV eye disease on vision was not incorporated in the model, and this could have had a significant impact on the estimated costs. Second, a longer time horizon would have been better to assess the long-term costs and benefits of acyclovir treatment. Finally, the use of quality-adjusted life-years would have been more informative in terms of cost-effectiveness ratios.

Implications of the study
The authors suggested that the decision to undergo prophylaxis treatment for the prevention of HSV eye disease should be made on a case-by-case basis. Future studies in ophthalmology should address specific issues, such as the assessment of quality of life information, which could be used in further economic evaluations.

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Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Acyclovir /economics /therapeutic use; Antiviral Agents /economics /therapeutic use; Cost-Benefit Analysis; Decision Trees; Drug Costs; Health Services Research; Humans; Keratitis, Herpetic /economics /prevention & control; Models, Economic; Premedication; Secondary Prevention; United States