The management of actinic keratoses in the United States with topical fluorouracil: a pharmacoeconomic evaluation
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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
The use of topical fluorouracil for the treatment of facial actinic keratoses (AKs). The creams contained 5% fluorouracil (Efudex), 1% fluorouracil (Fluoroplex) and 0.5% fluorouracil (Carac). Treatment regimens approved by the US Food and Drug Administration were considered. Non-approved topical fluorouracil regimens and combination regimens of topical fluorouracil with other treatments were not assessed.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of people with facial AKs. Studies of people with albinism, xeroderma pigmentosa and other "unique" populations were excluded. No further details of the study population were given.

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

Dates to which data relate
The studies included in the review of effectiveness were published between 1965 and 2001. The dates to which the resource use data related were not stated. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of completed studies.

Modelling
A multistep decision tree model was used to undertake a cost-effectiveness analysis with data from a variety of sources. The steps of the model included stating the aim of the study, identifying drug and resource use, determining the rate of efficacy of the comparators, performing a base-case analysis, and conducting a sensitivity analysis.

Outcomes assessed in the review
The efficacy outcomes used as input parameters for the model were lesional response and complete patient response (cure rate). Adverse events were not reported.
Study designs and other criteria for inclusion in the review
The included study designs were not reported. The included studies may have either been uncontrolled studies or the results for the comparator group were not reported.

Sources searched to identify primary studies
MEDLINE was searched for published English language literature using the search terms 'actinic keratoses', 'actinic keratosis' and 'management'. The reference lists of retrieved studies were also searched.

Criteria used to ensure the validity of primary studies
No validity assessment criteria were reported. Studies were excluded if the efficacy rates could not be extracted from the data presented.

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

Number of primary studies included
Seven published studies were included in the review.

Methods of combining primary studies
The results of the primary studies were combined in a meta-analysis, using the method of DerSimonian and Laird (see Other Publications of Related Interest) with a modification for single-group analysis. A weighted average efficacy rate with a 95% confidence interval (CI) was produced.

Investigation of differences between primary studies
The author did not investigate differences between the primary studies. Both cream and ointment formulations were considered in the meta-analysis.

Results of the review
Lesional response (reported in 3 studies) ranged from 83.1 to 100%. The average lesional response rate calculated by the meta-analysis was 87.8% (95% CI: 83.5 - 92.1).

The patient cure rate (reported in 7 studies) ranged from 0 to 100%. The average patient cure rate calculated by the meta-analysis was 62.5% (95% CI: 38.8 - 86.2).

Measure of benefits used in the economic analysis
The primary outcome measure used in the economic analysis was lesional response of cured facial AK. The costs were also calculated on the basis of patients cured of facial AKs.

Direct costs
Discounting was not carried out, but this was appropriate since the time period of the study was one year. The quantities and the costs were analysed separately. The quantities of resources used were derived after consultation with dermatologists and market researchers. They included the number of physician visits per year, number of treatment courses per year and use of cryotherapy. The consultation exercise appears to have taken place in the year 2000.

The average costs were obtained from the 2000 Drug Topics Red Book, Current Procedural Terminology (2000) and the Calendar Year 2000 Medicare Physician Fee Schedule. The analysis also included the direct costs of medical
management to the health service. These were for the initial visit, first follow-up visit, second follow-up visit, drug (for 1 - 6 lesions and more than 6 lesions), first treatment during calendar year (for 1 - 6 lesions and more than 6 lesions), two treatments per calendar year (for 1 - 6 lesions and more than 6 lesions). The cost of medical management included the payer's reimbursement rates for the initial consultation and two follow-up visits. The cost of the regimen was the sum of the drug acquisition and medical management costs. The drug acquisition cost was calculated according to the dosing schedule for that agent and the average wholesale price. It was assumed that the topical 5-fluorouracil cream was applied according to the directions on the respective package inserts. The costs of treating adverse effects were not included.

Statistical analysis of costs
The data for resource use and costs appear to have been deterministic.

Indirect Costs
No indirect costs were reported.

Currency
US dollars ($).

Sensitivity analysis
The cost of therapy per cured AK (lesional response) and the cost of therapy per patient cured of AK (patient response) were calculated for a patient with 1 to 20 AKs, for each of the treatment modalities.

Estimated benefits used in the economic analysis
The benefits used in the economic analysis were the efficacy results for lesional response rate and cure rate.

Cost results
The costs of one topical fluorouracil treatment per year were $218.18 (1 - 6 lesions) and $320.31 (more than 6 lesions) with the 5% cream, $191.66 (1 - 6 lesions) and $267.27 (more than 6 lesions) with the 1% cream, and $211.05 (1 - 20 lesions) with the 0.5% cream.

The costs of two topical fluorouracil treatments per year were $300 (1 - 6 lesions) and $440.43 (more than 6 lesions) with the 5% cream, $263.53 (1 - 6 lesions) and $367.50 (more than 6 lesions) with the 1% cream, and $290.19 (1 - 20 lesions) with the 0.5% cream.

Further detailed breakdowns of the cost were provided in the paper.

Synthesis of costs and benefits
The base-case evaluated the cost of treating a patient with 7 to 20 facial AKs twice in one calendar year, based on the lesional response rate.

On the basis of the lesional response of cured facial AKs, the base-case costs were $501.62 with the 5% cream, $418.56 with the 1% cream, and $330.52 with the 0.5% cream. On the basis of the patient cure rates, the base-case costs were $704.68 with the 5% cream, $587.99 with the 1% cream, and $464.31 with the 0.5% cream.

From the sensitivity analysis, the costs based on the lesional response rate of cured facial AK were:

for one treatment per year, $248.50 (1 - 6 lesions) and $364.82 (more than 6 lesions) with the 5% cream, $218.29 (1 - 6 lesions) and $304.41 (more than 6 lesions) with the 1% cream, and $240.38 (1 - 20 lesions) with the 0.5% cream;
for two treatments per year, $341.68 (1 - 6 lesions) and $501.62 (more than 6 lesions) with the 5% cream, $300.15 (1 - 6 lesions) and $418.56 (more than 6 lesions) with the 1% cream, and $330.52 (1 - 20 lesions) with the 0.5% cream.

From the sensitivity analysis, the costs based on patients cured of facial AKs were:

for one treatment per year, $349.09 (1 - 6 lesions) and $512.50 (more than 6 lesions) with the 5% cream, $306.66 (1 - 6 lesions) and $427.63 (more than 6 lesions) with the 1% cream, and $337.68 (1 - 20 lesions) with the 0.5% cream;

for two treatments per year, $480.00 (1 - 6 lesions) and $704.68 (more than 6 lesions) with the 5% cream, $421.65 (1 - 6 lesions) and $587.99 (more than 6 lesions) with the 1% cream, and $464.31 (1 - 20 lesions) with the 0.5% cream.

Authors' conclusions
For one treatment cycle, the average efficacy rates of a topical fluorouracil treatment were 87.8% based on lesional response or 62.5% based on patient cure. For more than 6 actinic keratoses (AKs), 0.5% fluorouracil cream may be more cost-effective than the 1% and 5% formulations. The true costs of therapy were underestimated, as the costs of treating adverse events were not included. However, the study suggests that once-daily use of 0.5% fluorouracil cream is a cost-effective way of treating a patient with multiple facial AKs.

CRD COMMENTARY - Selection of comparators
No comparators were assessed. The different formulations of 5-fluorouracil cream were compared only with one another. It may have been useful to compare the cream to cryotherapy, as the author states that this is used to treat two thirds of people with AKs.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from a review of published studies. The author did not state that a systematic review of the literature had been undertaken, although a meta-analysis was used to combine efficacy estimates from the included studies. It was not clear whether this was appropriate, as the author did not provide details of the study design or settings. No attempt was made to take account of differences between the studies (apart from the strength of topical 5-fluorouracil cream used). The meta-analysis was described briefly. The author stated that the method of DerSimonian and Laird (random-effects) was used to combine the results from published studies, but did not state whether the response rates were presented as odds ratios or risk ratios. Details of the review process, such as how many reviewers selected the studies and extracted the data, were not reported. The adverse effects of the interventions were not assessed, but were clearly relevant.

Validity of estimate of measure of benefit
The estimation of benefit was obtained directly from the effectiveness review. The choice of the estimate was not explicitly justified, but it appears to have been appropriate.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted seem to have been included in the analysis. The costs and the quantities were reported separately. The resource use quantities were derived from a consultation exercise. However, a sensitivity analysis of the quantities was not conducted. This may limit the interpretation of the study's findings. The prices were taken from published sources. The author pointed out wide variations in costs across the USA, but did not conduct a sensitivity analysis of the prices. Discounting was unnecessary since all the costs were incurred in one year. The price year was given, which enables reflation exercises to other settings.

Other issues
The author did not make appropriate comparisons of the findings with those from other studies. The issue of generalisability to other settings was not addressed. The author does not appear to have presented the results selectively.
It is not clear whether the author's conclusions reflect the scope of the analysis, as few details of the participants in the included studies were given. The author reported a further limitation in that the costs of treating adverse events were not included.

**Implications of the study**
The results tend to support the use of 0.5% fluorouracil cream once daily. The author, however, does not make any clear recommendations for changes in policy or practice, or for further research.

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None stated.

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12353678

**Other publications of related interest**

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Subject indexing assigned by NLM

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