Effectiveness of 5-fluorouracil treatment for actinic keratosis: a systematic review of randomized controlled trials

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CRD summary
The review evaluated the safety and effectiveness of the use of 5-fluorouracil in the treatment of actinic keratosis and found it effective in reducing mean/median lesion count and total lesion count, and providing complete clearance in some patients. The limitations of the review process and the evidence provided imply that the authors’ conclusions should be interpreted with caution.

Authors’ objectives
To evaluate the safety and effectiveness of 5-fluorouracil in the treatment of actinic keratosis.

Searching
MEDLINE (from 1966), EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to January 2008 for studies in English. Search terms were not reported. The bibliographies of each retrieved article were hand searched.

Study selection
Randomised controlled trials (RCTs) that compared treatment of actinic keratosis using 5-fluorouracil (5-FU) with placebo or another active treatment, or that investigated different 5-FU dosage regimens, were eligible for inclusion. Participants were not required to have a histological diagnosis for inclusion (clinical diagnosis was sufficient).

5-FU was compared to placebo, facial resurfacing with carbon dioxide laser or 30% trichloroacetic acid peel, imiquimod, cryotherapy, diclofenac sodium 3% gel (DFS), 5-aminolevulinic acid (ALA) photodynamic therapy (PDT) (activated with either blue light, red light, or pulsed laser light), 5-FU augmented with tretinoin and placebo. Most included studies used 5% 5-FU; other studies used 0.5% 5-FU. One study compared different 5-FU regimes. Duration of interventions ranged from one week to 16 weeks. Participants in most of the included studies had actinic keratosis lesions on the face or scalp. Mean number of lesions (where given) ranged from more than three to 17.5. Mean age ranged from 62 to 73 years. The proportion of males ranged from 47% to 95%.

Eligible outcomes were not specified, but the outcomes measured included absolute and proportional changes in lesions counts per patient, changes in total lesion count, change in lesion area, tolerability, and patient preferences. The authors considered that complete healing of lesions treated with 5-FU required two months after cessation of treatment, but assessment was short (four weeks) in half the included RCTs.

Two independent researchers performed the study selection. The authors did not state how disagreements were resolved.

Assessment of study quality
Study quality was assessed according to the following criteria: random sequence generation; allocation concealment; blinding; objectiveness of outcome assessment; completeness of follow-up; use of intention-to-treat analysis (ITT); occasions of selective reporting; and objectiveness of outcome measures.

The authors did not report how many reviewers performed the validity assessment.

Data extraction
Data were extracted on the number of patients with complete clearance of lesions and for changes in the mean number of lesions. Mean differences and 95% confidence intervals (CI) were calculated for continuous data. Odds ratios (OR) and 95% CI were calculated for dichotomous data.
The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**
A narrative synthesis was provided.

**Results of the review**
Thirteen RCTs were identified (n=864, range 17 to 207). Most RCTs were poorly reported, most were small and most had a moderate to high risk of bias: only five RCTs provided details of randomisation method, two of which adequately described allocation concealment; one RCT was double-blind and four RCTs were single-blind; only five RCTs performed intention-to-treat analysis; and eight RCTs provided incomplete data. Three RCTs had sufficient power.

There was a significantly greater reduction in mean/median number of lesions (RML) for 0.5% 5-FU compared to placebo (MD 4.8, 95% CI 3.1 to 6.5; one RCT). There was no difference in reduction in mean/median number of lesions with 5% 5-FU compared to 5% 5-FU augmented with tretinoin (one RCT), resurfacing with carbon dioxide laser (one RCT) and 30% trichloroacetic acid peel (one RCT). Treatment with 5% 5-FU significantly increased the number of patients with 100% clearance of lesions compared to cryotherapy (OR 10.8, 95% CI 1.2 to 94.9; one RCT). Treatment with 0.5% 5-FU significantly increased the number of patients with 100% clearance of lesions compared to ALA PDT activated by pulsed laser light (OR 11.0, 95% CI 1.1 to 114.1; one RCT) or placebo (OR 30.0, 95% CI 1.7 to 516.5; one RCT). Comparative data were not available for the reduction in the total number of lesions.

One RCT found no difference in cosmetic outcomes at three months, but at 12 months 81% patients treated with imiquimod had an excellent cosmetic outcome (based on scarring, atrophy and induration) compared to 4% of patients treated with 5% 5-FU or cryotherapy. Two RCTs reported on patient preferences for treatment. One RCT found 85% patients preferred 0.5% 5-FU compared to 15% patients who preferred 5% 5-FU. Another RCT found 79% patients were very or completely satisfied with DFS compared to 68% who had the same level of satisfaction with 5% 5-FU. Withdrawal due to adverse events was reported in three RCTs. A greater proportion withdrew from treatment with 5% 5-FU (5.9%) than 0.5% 5-FU (1.9%). Four RCTs reported on early cessation of treatment and gave values of 4%, 11%, 17% and 86% for 5-FU.

**Authors’ conclusions**
Treatment with 5-FU for actinic keratosis lesions gave complete clearance in about half of patients, 80% reduction in mean/median lesion count and 90% reduction in total lesion count. Most patients (about two-thirds) required re-treatment after one year. Few patients stopped treatment as a result of adverse effects. Up to one half of patients may not be able to complete their course of treatment. The quality of the studies that provided the evidence was poor. Evidence on alternative treatments was limited.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions and study design. Eligible outcomes were not clearly defined. Relevant databases were searched. No specific attempts were made to locate unpublished studies and the review was restricted to English-language studies, so there was a possibility of language and publication biases. Publication bias was not assessed. Study quality was assessed using suitable criteria. Although study selection was carried out independently by two reviewers, it was unclear how disagreements were resolved. It was unclear whether efforts were made to reduce error and bias in other aspects of the review process. Relevant study details were reported, but there was a lack of statistical results. The authors stated that a narrative synthesis was presented as outcomes were considered too heterogeneous for pooling. The synthesis was unstructured and confusing. The authors commented that the assessment period was too short in seven of the 13 included studies since complete healing required two months after cessation of treatment. In view of some potential limitations arising from the reporting of the review process, lack of clarity in the authors’ overall conclusions, possibility of missed studies and the inappropriate length of some studies, the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.
Research: The authors identified a need for further studies with sufficient power, study designs that avoided bias and robust outcome measurement. Studies should accurately trace the evolution of all lesions included at baseline. Studies should identify the characteristics of the actinic keratosis lesions that were most or least likely to be cured. Evidence was needed to help clinicians chose between 5-FU and imiquimod and other treatment modalities, and find the long-term effectiveness of treatment. Evidence on patient satisfaction was required to enable patients to make informed choices.

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