Comparison of topical 5-fluorouracil formulations in actinic keratosis treatment

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CRD summary
The authors concluded that there was inadequate information to formulate a decision on the comparative efficacy of 0.5% and 5% 5-fluorouracil in patients with multiple actinic keratoses of the face and scalp. The synthesis suffered from significant limitations that provided a substantial threat to the overall reliability of the review.

Authors' objectives
To evaluate the efficacy of 0.5% and 5% 5-fluorouracil cream monotherapy to treat patients with multiple actinic keratoses of the face and scalp.

Searching
PubMed and EMBASE were searched from 1965 to April 2009 for articles in English. Some search terms were reported.

Study selection
Randomised controlled trials (RCTs) that assessed 0.5% 5-fluorouracil once daily for one to four weeks and/or 5% 5-fluorouracil twice daily for two to four weeks in patients with multiple actinic keratoses on the face, ears, neck and/or scalp were eligible for inclusion. No inclusion criteria were specified for comparison groups. Patients were required to have no other medications than mild topical corticosteroids.

Comparison groups received aminolevulinic acid activated with blue light or pulsed dye laser, vehicle cream, cryosurgery, 1% 5-fluorouracil cream, interferon alpha 1b injectable and 5% imiquimod. The primary outcome of interest was complete clearance of all actinic keratoses (no clinically visible actinic keratoses in the treatment area) at four weeks post-treatment for 0.5% 5-fluorouracil and at four to six weeks post-treatment for 5% 5-fluorouracil. Adverse events were reported.

The authors did not state how many reviewers selected studies.

Assessment of study quality
There was no reported validity assessment of included studies.

Data extraction
Data were extracted on the number/percentage of patients with complete clearance at follow-up.

The authors did not state how many reviewers carried out data extraction.

Methods of synthesis
A narrative synthesis was presented. Study details and results were summarised in tables.

Results of the review
Nine studies (n=841 participants) were included in the review. Seven studies were described as RCTs, one was a controlled clinical trial and one was a comparative study. Four studies were double-blind.

For 0.5% 5-fluorouracil the rate of complete clearance ranged from 14.9% (one week post treatment) to 57.8% (four weeks post treatment). For 5% 5-fluorouracil, complete clearance rates ranged from 43% (four weeks post treatment) to 100% (two weeks post treatment).

One RCT (n=21) that provided a direct comparison between 0.5% and 5% 5-fluorouracil demonstrated equivalent complete clearance rates (43%) and a higher rate of facial irritation for 5% 5-fluorouracil.
Adverse events included erythema, pain and burning, mild to moderate facial irritation and other application site reactions. Use of various measures of tolerability precluded comparisons of adverse events between the two treatment regimens.

**Authors’ conclusions**

There was inadequate information to formulate a conclusion on the comparative efficacy of 0.5% and 5% 5-fluorouracil in patients with multiple actinic keratoses of the face and scalp.

**CRD commentary**

The review question was clear and supported by reproducible inclusion criteria, although comparators were not specified. The search strategy was limited to two electronic databases and restricted to articles in English, so studies may have been missed and language bias could not be ruled out. There was no specific search for unpublished studies and this raised the possibility of publication bias. It was unclear whether or not any part of the review process contained efforts to minimise error and bias. There was no reported validity assessment of the included studies. The clinical variability among the included studies made a narrative synthesis appropriate.

The synthesis suffered from significant limitations. Each arm of the trial was treated as a separate case-series, so the randomisation within studies was lost and comparison groups were ignored. This represents a substantial threat to the overall reliability of the review.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further high-powered clinical trials should compare 5-fluorouracil formulations with each other and with other treatments. Accurate and reproducible methods of lesion counts were required. Further examination of tolerability rates was required.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.