Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials

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CRD summary
This review assessed the effects of using oral retinoids to prevent skin cancers in recipients of solid organ transplants. The authors concluded that limited data from a few small studies suggest that acitretin may prevent new skin cancers, but the drug is poorly tolerated. This was a well-conducted review and the authors' cautious conclusions reflect the limited evidence.

Authors' objectives
To assess the effects of oral retinoids in the prevention of skin cancers in patients who have received solid organ transplants.

Searching
MEDLINE (1966 to October 2003), EMBASE (1980 to week 44, 2003) and the Cochrane Controlled Trials Register (Issue 3, 2003) were searched using the reported terms. Non-English abstracts were also considered. Reference lists were checked and an expert in the field was contacted for additional studies. Unpublished data and data from pharmaceutical companies were not included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-RCTs were eligible for inclusion.

Specific interventions included in the review
Studies of any dose, formulation or duration of oral retinoids used for the prevention of skin cancers were eligible for inclusion. The included studies compared acitretin with placebo, no treatment or another dose of acitretin; the doses and regimens varied between studies (25 to 30 mg daily and 0.2 or 0.4 mg/kg per day). All of the studies were set in university teaching hospitals. The treatment lasted for 6 to 12 months.

Participants included in the review
Studies of patients of any age or ethnicity who had received a solid organ transplant were eligible for inclusion, whether or not they had a history of skin cancers. All of the included studies were in adult Caucasian patients who had received a renal transplant on average 10 to 15 years before. All of the studies excluded patients with pregnancy, hyperlipidaemia, increased alcohol intake and impaired renal or hepatic function.

Outcomes assessed in the review
The primary review outcome was the number of skin cancers, including squamous cell carcinomas (SCCs), basal cell carcinomas (BCCs) and melanoma. Other review outcomes were the number of premalignant lesions and adverse effects. The included studies detected skin cancers by clinical examination and adverse effects by clinical history and laboratory tests.

How were decisions on the relevance of primary studies made?
One reviewer conducted the searches and two reviewers independently selected studies from the titles and abstracts identified.

Assessment of study quality
Studies were assessed for method of randomisation, allocation concealment, blinding, completeness of follow-up,
withdrawals and intention-to-treat analysis. Two reviewers independently assessed validity and any disagreements were resolved by discussion.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Differences in the number of observed outcomes between the groups were reported, along with 95% confidence intervals (CIs) and significance levels where available.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative. Each study was described in the text, with additional descriptive information presented in the accompanying tables.

How were differences between studies investigated?
Differences between the studies were discussed in the text.

Results of the review
Three controlled trials (n=93) were included: two parallel-group trials (n=70) and one crossover trial (n=23).

In terms of study quality, none of the trials reported the method of randomisation. One trial used triple-blinding; the other two trials were open label. Two trials analysed patients on an intention-to-treat basis; the other performed a per protocol-based analysis.

New skin cancers.
The two studies comparing acitretin with placebo or no treatment found a significant reduction in the number of new skin cancers compared with control: 18 with acitretin versus 2 with control (P=0.009) in one trial and 46 SCCs versus 65 SCCs during the drug-free period (P=0.002) in the crossover trial. A statistically significant reduction in the numbers developing BCC was also noted (P=0.045). One of the trials also found a significant reduction in the number of patients developing new skin cancer (2 out of 19 versus 9 out of 19 for the control, P=0.01). The other trial found a reduction in the number of patients with skin cancer during acitretin treatment compared with the drug-free period, but the statistical significance was not reported (6 developed SCCs during acitretin treatment, while 15 developed SCCs during the drug-free period).

The third trial found no significant difference between high- and low-dose acitretin in the number of new malignant lesions. However, no details on the actual numbers of tumours were available.

Premalignant lesions.
Two trials assessed the reduction in premalignant lesions with acitretin. One found a reduction of 13.4% with acitretin versus an increase of 28.2% with the control (P=0.008), while the other found reductions with both high- and low-dose acitretin after 2 months (P<0.0001) compared with the situation before acitretin treatment.

Adverse events.
The rates of withdrawal due to adverse events were relatively high: 21% in one trial, 39% in a second, and 7% with high-dose and 8% with low-dose acitretin in the third. Adverse events leading to withdrawal included rash, hyperlipidaemia, dysphagia due to stomach cancer, headaches, paronychia, elevated serum liver enzymes, musculoskeletal complaints, gastritis and mucocutaneous effects. Cheilitis was common (70 to 100%) in patients continuing with treatment. Other tolerated adverse effects included alopecia (44 to 47%), headache (40%), myalgia (20 to 35%), rash (30%), photosensitivity (30%), dry eyes (30%), palmoplantar desquamation (20%), epistaxis (20%), nail changes (15%) and pruritus (10%).
None of the trials reported a worsening of renal or liver function.

**Authors’ conclusions**
Limited data from a small number of trials suggest that acitretin may prevent new skin cancers in recipients of solid organ transplants, but the use of acitretin may be limited by poor tolerability.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Three relevant databases were searched and the authors acknowledged the potential for publication bias resulting from their decision to exclude unpublished data. Language bias was addressed. Methods were used to minimise errors and bias at the study selection and validity assessment stages, but it was not explicitly reported whether similar steps were taken for the data extraction. Validity was assessed and the results of the assessment were reported. The included studies were adequately described. Combining the studies in a narrative was appropriate given the differences between the studies, and the synthesis took study quality into account. Overall, this was a well-conducted review and the authors’ cautious conclusions reflect the limited evidence.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should seek to identify subgroups of patients most likely to benefit from oral retinoids; should assess the effects of retinoids in patients who have received solid organ transplants other than kidneys; and should assess the effects of retinoids for primary prevention. The development of alternative drugs with improved safety profiles is also needed.

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