Combination regimens of topical calcipotriene in chronic plaque psoriasis: systematic review of efficacy and tolerability

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Authors' objectives
To examine the efficacy and tolerability of calcipotriene combined with phototherapy or systemic therapies, compared with monotherapy, for the treatment of chronic plaque psoriasis.

Searching
MEDLINE, EMBASE, BIDS Index to Scientific and Technical Proceedings, and the Cochrane Controlled Trials Register were searched from 1987 to January 1999 using the following textwords: 'calcipotriol', 'MC903', 'calcipotriene', 'Dovonex', 'Daivonex' and 'Psorcutan'. This strategy was supplemented by searching the information database maintained by the manufacturer of calcipotriene (Leo Pharmaceuticals, UK) and the reference lists of all retrieved RCTs. Trials in any language were considered.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
The inclusion criteria specified that studies must be of the efficacy or tolerability of calcipotriene (0.005% cream or ointment) when combined with phototherapy or systemic antipsoriatic therapies.

The included studies fell into five categories:

1. Calcipotriene (twice daily or 100 g per week) plus UV-B phototherapy (3 to 5 times per week) versus calcipotriene (twice daily or 100 g per week).

2. Calcipotriene (twice daily or 100 g per week) plus UV-B phototherapy (2 to 3 times per week) versus placebo (none or twice daily) plus UV-B phototherapy (3 times per week).

3. Calcipotriene (twice daily) plus psoralen-UV-A (2 to 4 times per week) versus placebo (twice daily) plus psoralen-UV-A (2 to 4 times per week).

4. Calcipotriene (twice daily) plus acitretin versus placebo (twice daily) plus acitretin.

5. Calcipotriene (twice daily) plus cyclosporine versus placebo (twice daily) plus cyclosporine.

Participants included in the review
Studies of patients with chronic plaque psoriasis were eligible for inclusion in the review. The exclusion criteria included guttate, pustular, or erythrodermic psoriasis.

Outcomes assessed in the review
The patient's overall assessment of response was the primary outcome measure.

The efficacy criteria were:

1. The proportion of patients showing marked improvement or clearance in patient and investigator overall assessments of response.

2. The proportion of patients with clearance in patient and investigator overall assessments of response.
3. The mean percentage change from baseline in the Psoriasis Area Severity Index (PASI; see Other Publications of Related Interest no.1).

The proportion of patients experiencing cutaneous, noncutaneous and any other adverse effects, and the number of withdrawals due to adverse effects, were also examined.

How were decisions on the relevance of primary studies made?
Two authors assessed the eligibility of primary studies, on the basis of their abstracts.

Assessment of study quality
The authors did not state that they assessed validity. However, only RCTs were included in the review.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The data were extracted on study design, mean patient age, the duration of treatment and follow-up, nature of treatment and control, the number of patients in the treatment and control groups, outcomes, adverse events, and withdrawal rates.

For dichotomous outcomes, efficacy was estimated using the rate ratio (RR), defined as the proportion of patients achieving the outcome in the treatment group relative to the control group. Adverse events were estimated on the basis of the RR (or relative risk) and the rate difference. When there were no events in one group, the review's authors added 0.5 to each of the cells of the 2x2 table. In all cases, an intention to treat analysis was used. The Rothman method was used to estimate the 95% confidence intervals for the individual RRs and the rate difference (see Other Publications of Related Interest no.3).

For continuous outcomes, the percentage change in PASI from baseline was analysed using the weighted mean difference. This was defined as the difference between mean values in the treatment and control groups for individual trials, and the mean difference weighted for trial size for groups of trials (see Other Publications of Related Interest no.2). In estimating the weighted pooled difference in effect, the inverse of the squared sample variance of the difference in response was used as the weight.

Methods of synthesis
How were the studies combined?
The method of DerSimonian and Laird (see Other Publications of Related Interest no.4), as implemented by Whitehead and Whitehead (see Other Publications of Related Interest no.5), was used to calculate pooled effect estimates and their corresponding 95% CIs. If there was no evidence of statistical heterogeneity, summary estimates of the effect from each trial were pooled using a fixed-effect model. A random-effects model was used if the P value was less than or equal to 0.05.

How were differences between studies investigated?
Heterogeneity between trials was investigated using chi-squared tests, where a P value equal to or less than 0.05 indicated significant heterogeneity.

Results of the review
Eleven RCTs were included in the review: 1 was a three-armed parallel group study, and 10 were two-armed head-to-head comparisons. [AC:Five of the latter were bi-lateral comparisons]. This represented a total of 756 patients randomised to treatment. Four trials were double-blind (388 participants), 2 were single-blind (177 participants) and 5 were open (191 participants).

When using the outcome of PASI, the antipsoriatic effects of acitretin, cyclosporine, and psoralen-UV-A phototherapy were enhanced by the addition of topical calcipotriene. This did not, however, translate into an increase in the number of patients who achieved at least marked improvement. At the end of treatment, the RRs for marked improvement or
clearance in patient assessments were:

- for calcipotriene plus acitretin versus acitretin alone (12 weeks), 1.4 (95% CI: 1.0, 1.9);
- for calcipotriene plus cyclosporine versus cyclosporine alone (6 weeks), 1.2 (95% CI: 0.9, 1.6); and
- for calcipotriene plus psoralen-UV-A versus psoralen-UV-A alone (12 weeks), 1.2 (95% CI: 0.9, 1.6).

Patients were also no more likely to obtain at least marked improvement with calcipotriene plus UV-B therapy than with UV-B therapy alone (RR 1.0, 95% CI: 0.8, 1.1) at 8 weeks in the patient assessment. There was limited evidence that the use of calcipotriene might reduce the cumulative exposure to phototherapy and systemic treatment. During the short duration of these trials, there were no significant differences in withdrawal rates or adverse effects between the combined regimens and their corresponding monotherapy control interventions.

Authors' conclusions
Overall, there was insufficient evidence to support any large effects in favour of combination treatment. In the patient assessments, the results did not show an adjuvant effect, but there was some evidence that the use of calcipotriene may reduce cumulative exposure to systemic therapy to obtain clearance. There were no long-term morbidity data on the effectiveness of any of the combinations studied. Given that psoriasis is a chronic recurrent disease for most patients, trials of longer duration are needed to determine whether the addition of topical calcipotriene to systemic therapies improves the risk-benefit ratio by reducing the long-term risk of toxic effects. Equally important is the need to examine the impact of such combinations on the duration of remission after treatment.

CRD commentary
The review question was clearly defined, and the predefined inclusion and exclusion criteria were applied rigorously. The search strategy was comprehensive and thorough, though attempts to identify unpublished data were limited to a search of the Cochrane Controlled Trials register [AC:and an in-house database maintained by the manufacturer]. There was no formal assessment of publication bias.

The methodological validity of the primary studies was not assessed, although the included studies were restricted to RCTs. Complete details of the methods used, and the treatment regimens of the individual primary studies, were provided. However, details of the included participants were minimal, i.e. age and clinical condition only. It was therefore difficult to determine the extent to which the results of this review may apply to the general population of patients with chronic plaque psoriasis. There were also discrepancies about the total number of participants included in the review.

The studies were appropriately combined and the results were clearly presented. The authors' conclusions follow clearly from the results. Attention was drawn to the limitations of the review, more specifically, the small number of robust clinical trials available for inclusion and the lack of a standard clinical outcome measure for improvement in psoriasis.

Implications of the review for practice and research
Practice: The authors state that topical calcipotriene has not been shown to substantially enhance the effect of systemic therapy. There were relatively few studies, and it is possible that small additive effects of calcipotriene could have been missed. The magnitude of the observed effect suggests that the response is not of clinical relevance to the patient.

Research: The authors state that longer trials are needed to establish whether the use of topical calcipotriene improves the risk-benefit ratio of systemic treatment by reducing the long-term risks of toxic effects, and also to examine whether there is a dose sparing effect.

Future studies should also investigate whether the use of topical calcipotriene prolongs the duration of remission. Since psoriasis is a chronic disease for most patients, differences in remission time after treatment may be a more important...
measure of a treatment’s relative efficacy than differences in the clearing capacity. The authors proposed that the time to relapse would be a useful outcome measure, but to enable the direct comparison of results from different trials, the definition of relapse would need to be precisely defined and universally agreed on.

Other topical agents besides calcipotriene have also been shown to be effective adjuvant therapies in severe psoriasis. In recent years, anthralin, tacalcitol and tazarotene have been reported to improve the outcome of second-line treatments; their risk-benefit profile should be compared with that of calcipotriene.

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