Combination Regimens of Topical Calcipotriene in Chronic Plaque Psoriasis

Systematic Review of Efficacy and Tolerability

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Objective: To examine the efficacy and tolerability of calcipotriene combined with phototherapy or systemic therapies compared with monotherapy for the treatment of chronic plaque psoriasis.

Design: Quantitative systematic review of 11 randomized controlled trials involving a total of 756 patients with plaque psoriasis.

Main Outcome Measures: Rate ratios (RRs) for marked improvement or clearance in patient and investigator overall assessments of response; mean difference in percentage change in Psoriasis Area and Severity Index; and RRs for clearance in patient and investigator overall assessments of response. Adverse effects were estimated with the RR and the rate difference in terms of withdrawal rate, proportion of patients experiencing adverse events, and proportion of patients with cutaneous and noncutaneous adverse effects.

Results: Antipsoriatic effects of acitretin, cyclosporine, and psoralen–UV-A phototherapy were enhanced with the addition of topical calcipotriene using the Psoriasis Area and Severity Index as the outcome, but this is not translated into an increase in the number of patients who achieve at least marked improvement. At the end of treatment, the RRs for marked improvement or clearance in patient assessments were as follows: calcipotriene plus acitretin vs acitretin alone (12 weeks), 1.4 (95% confidence interval [CI], 1.0-1.9); calcipotriene plus cyclosporine vs cyclosporine alone (6 weeks), 1.2 (95% CI, 0.9-1.6); and calcipotriene plus psoralen–UV-A vs psoralen–UV-A alone (12 weeks), 1.2 (95% CI, 0.9-1.6). Patients were also no more likely to obtain marked improvement or better 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 is limited evidence that 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.

Conclusions: Overall, there is insufficient evidence to support any large effects in favor of combination treatment. In the patient assessments, the results do not show an adjuvant effect, but there is some evidence that use of calcipotriene might 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, longer trials are needed to determine whether the addition of topical calcipotriene to systemic therapy 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.

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MATERIALS AND METHODS

INCLUSION AND EXCLUSION CRITERIA

The following selection criteria were used to identify studies for inclusion in this analysis.

**Types of Studies**

Only RCTs were included. Quality scoring was restricted to this threshold criterion because of broad support for the clinical importance of these items but less so on other items often included in quality scores.

**Types of Participants**

Patients with chronic plaque psoriasis were eligible for inclusion. Exclusion criteria included guttate, pustular, or erythrodermic psoriasis.

**Types of Interventions**

Calcipotriene, 0.005% cream or ointment, used in combination with phototherapy or systemic antipsoriatic therapies.

**Types of Outcome Measures**

**Assessment of Efficacy.** 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; and (3) the mean percentage change from baseline in the Psoriasis Area and Severity Index (PASI).

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

**SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES**

The RCTs were identified by computerized searches (from 1987) of the Cochrane Controlled Trials Register, EMBASE, MEDLINE, and the BIDS Index to Scientific and Technical Proceedings. Textwords applied to the search included calcipotriol, MC903, calcipotriene, Dovonex, Daivonex, and Psorcutan. This was supplemented by searching the information database maintained by the manufacturer of calcipotriene (Leo Pharmaceuticals, Buckinghamshire, England) and the reference lists of all retrieved RCTs. The search was most recently updated in January 1999. Trial eligibility was determined by 2 authors (D.M.A. and A.L.W.P. There were no language restrictions. Abstracts were considered; relevant information not included in the published reports was obtained by contacting the principal author of the trial or the manufacturer.

**METHODS OF REVIEW**

**Dichotomous Outcomes**

Efficacy was estimated with the rate ratio (RR), defined as the proportion of patients achieving the outcome in the treatment group relative to the control group. If the treatment makes no difference to the rate of events, the RR is 1. Beneficial interventions will have an RR greater than 1. A 95% confidence interval (CI) for the RR that crosses unity indicates that there was no significant difference in the rate of the outcome between the treatment groups (P> .05). Adverse effects were estimated with the RR (or relative risk) and the rate difference. When there were no events in 1 group we added 0.5 to each cell of the 2 × 2 table. In all cases, we used an intention-to-treat analysis, whereby the denominator was the number of patients randomized. The Rothman method was used for 95% CI estimation of the individual RR and rate difference.

**Continuous Outcomes**

The percentage change in PASI from baseline was analyzed as the weighted mean difference, 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. In estimating the weighted pooled difference in effect, the inverse of the squared SE (sampling variance) of the difference in response was used as the weight.

The method of DerSimonian and Laird was implemented by Whitehead and Whitehead. 7 was used to calculate the pooled estimates and their corresponding 95% CIs. Heterogeneity between trials was examined using χ² tests, with P ≤ .05 indicating significant heterogeneity. Heterogeneity refers to nonhomogeneous treatment effects from the different trials being considered. The statistical power of the χ² tests for heterogeneity is, in many cases, low because of the small number of combined trials. If there was no evidence of statistical heterogeneity, summary estimates of the effect from each trial were pooled using a fixed effects model. A random effects model was used if P ≤ .05. Results from fixed or random effects modeling are shown as appropriate in the tables and figures.

RESULTS

**CHARACTERISTICS OF ELIGIBLE TRIALS**

Eleven RCTs that met the study’s inclusion criteria were identified. In all, this represented 756 patients random-
ized to treatment. Table 1 shows details of these trials. One trial was a 3-armed parallel group study, and the remaining 10 trials were 2-armed head-to-head comparisons, 5 of which involved a bilateral (right/left) design. The duration of randomized treatment ranged from 2 to 12 weeks. Two non-English publications were retrieved. All trials were randomized and controlled. Five trials were open, 2 were single-blind, and 4 were double-blind. One trial did not report the variance of the percentage change in PASI from baseline, necessitating variance imputation.

### EFFICACY

Results of the efficacy analyses are shown in Figures 1, 2, 3, 4, and 5.

**Calcipotriene and UV-B Phototherapy**

Combined calcipotriene and UV-B phototherapy proved more effective than calcipotriene monotherapy on the basis of the proportion of patients whose psoriasis cleared and the mean difference in the percentage change in PASI. The RRs for clearance at 8 weeks were 2.1 (95% CI, 1.2-3.7) in the patient overall assessment and 2.3 (95% CI, 1.6-3.4) in the investigator overall assessment. Comparing the proportion of patients showing marked improvement or clearance, there was no significant difference between the combined regimen and calcipotriene alone. The RRs at 8 weeks were 1.1 (95% CI, 0.9-1.2) in both patient and investigator overall assessments. Comparing with UV-B monotherapy in one trial of 77 patients, there was no significant difference in response with a combined regimen of calcipotriene and UV-B (3 times weekly). The RRs for marked improvement or clearance at 8 weeks were 1.0 (95% CI, 0.8-1.1) in both patient and investigator overall assessments, whereas the corresponding RRs for clearance were 1.1 (95% CI, 0.7-1.8) and 1.0 (95% CI, 0.6-1.7), respectively. At the end of treatment (8 weeks), the mean difference in the percentage change in PASI was −1.9% (95% CI, −9.2% to 5.4%).

One trial of 164 patients compared calcipotriene and UV-B (2 times weekly) with placebo cream and UV-B (3 times weekly). The efficacy results were essentially similar between the 2 treatment groups. There was a significant difference only in the patient overall assessment of clearance; the RR at the end of treatment (12 weeks) was 0.6 (95% CI, 0.4-0.9). The mean difference in the percentage change in PASI was −4.1% (95% CI, −14.5% to 6.3%).

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**Table 1. Characteristics of Randomized Controlled Trials**

<table>
<thead>
<tr>
<th>Trial Description</th>
<th>Design</th>
<th>Patient Age, Mean, y</th>
<th>Treatment Duration, wk</th>
<th>Follow-up</th>
<th>Treatment</th>
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<td><strong>Calcipotriene + UV-B Phototherapy vs Calcipotriene</strong></td>
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<tr>
<td>Kragballe, 1990</td>
<td>Open-B</td>
<td>47</td>
<td>8</td>
<td>8 wk</td>
<td>CPT bid + UV-B (3×/wk)</td>
<td>CPT bid</td>
<td>20</td>
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<td>Molin et al, 1993</td>
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<td>43.7</td>
<td>8</td>
<td>8 wk</td>
<td>CPT bid + UV-B (3×/wk)</td>
<td>CPT bid</td>
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<td>Open-B</td>
<td>43.5</td>
<td>2</td>
<td>4 wk</td>
<td>CPT bid + UV-B (5×/wk)</td>
<td>CPT bid</td>
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<tr>
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<td>Open-P</td>
<td>40</td>
<td>4</td>
<td>4 wk</td>
<td>CPT 100 g/wk + UV-B (3×/wk)</td>
<td>CPT 100 g/wk</td>
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<tr>
<td>Molin, 1997</td>
<td>DB-B</td>
<td>46.9</td>
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<td>4 wk</td>
<td>CPT 100 g/wk + UV-B (3×/wk)</td>
<td>Vehicle bid + UV-B (3×/wk)</td>
<td>10</td>
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<td>Ramsay, 1998</td>
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<td>12</td>
<td>12 wk</td>
<td>CPT bid + UV-B (2×/wk)</td>
<td>Vehicle bid + UV-B (3×/wk)</td>
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<td>Frappaz and Thivolet, 1993</td>
<td>DB-P</td>
<td>46.2, 47</td>
<td>12</td>
<td>6 mo</td>
<td>CPT bid + PUVA (3×/wk)</td>
<td>Vehicle bid + PUVA (3×/wk)</td>
<td>54</td>
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<td>Speight and Farr, 1994</td>
<td>SB-B</td>
<td>50</td>
<td>6</td>
<td>6 wk</td>
<td>CPT bid + PUVA (2×/wk)</td>
<td>Vehicle bid + PUVA (2×/wk)</td>
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<tr>
<td><strong>Calcipotriene + Acitretin vs Placebo + Acitretin</strong></td>
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<tr>
<td>van de Kerkhof et al, 1998</td>
<td>DB-P</td>
<td>48.1, 47.1</td>
<td>12</td>
<td>12 wk</td>
<td>CPT bid + acitretin</td>
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<td><strong>Calcipotriene + Cyclosporine vs Placebo + Cyclosporine</strong></td>
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<tr>
<td>Grossman et al, 1994</td>
<td>DB-P</td>
<td>44.2, 43.3</td>
<td>6</td>
<td>6 mo</td>
<td>CPT bid + cyclosporine</td>
<td>Placebo bid + cyclosporine</td>
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* Open-B indicates open, bilateral comparison; Open-P, open, parallel group; DB-B, double-blind, bilateral comparison; DB-P, double-blind, parallel comparison; SB-P, single-blind, parallel group; SB-B, single-blind, bilateral comparison; CPT, calcipotriene, 50 µg/g; bid, twice daily; PUVA, psoralen–UV-A; and ellipses, no follow-up.

† Three-armed trial.
Calcipotriene and Psoralen–UV-A Therapy

Three trials compared calcipotriene and psoralen–UV-A (PUVA) with placebo ointment and PUVA in 140 patients. There was no significant difference in the proportion of patients reporting marked improvement or clearance in the patient assessment; the RR at 12 weeks was 1.2 (95% CI, 0.9-1.6). The corresponding RR for clearance was 2.1 (95% CI, 1.0-4.2). In contrast, the PASI results showed an improved response to PUVA with calcipotriene. At the end of treatment (12 weeks), the mean difference in the percentage change in PASI was 15.7% (95% CI, 3.6%-27.8%).

Calcipotriene and Acitretin

One trial of 135 patients compared calcipotriene and acitretin with placebo ointment and acitretin. On the basis of the proportion of patients showing at least marked improvement and the percentage change in PASI, calcipotriene had a significant additional effect to acitretin at every assessment point during treatment. At the end of treatment (12 weeks), the RRs for marked improvement or clearance were 1.4 (95% CI, 1.0-1.9) in the patient assessment and 1.6 (95% CI, 1.2-2.3) in the investigator assessment. The mean difference in the percentage change in PASI was 23.3% (95% CI, 9.8%-36.8%). In contrast, the RRs for clearance at 12 weeks in patient and investigator overall assessments were equal at 7.0 (95% CI, 0.9-53.6).

Calcipotriene and Cyclosporine

One trial compared calcipotriene and cyclosporine with placebo ointment and cyclosporine in 69 patients. The calcipotriene and cyclosporine combination was significantly more effective than placebo and cyclosporine on the basis of the proportion of patients cleared and the percentage change in PASI. At the end of treatment (6 weeks), the RRs for clearance in patient and investigator overall assessments were 3.2 (95% CI, 1.1-8.7) and 3.9 (95% CI, 1.2-12.6), respectively, and the mean difference in the percentage change in PASI was 22.1% (95% CI, 7.4%-36.8%). There were no significant differences in the proportion of patients with marked improvement or clearance; the RRs were 1.2 (95% CI, 0.8-1.6) and 1.4 (95% CI, 1.0-1.9) in patient and investigator assessments, respectively.

WITHDRAWAL FROM TREATMENT

Table 2 summarizes the data for withdrawal from treatment for any reason and as a result of adverse effects. All the pooled RRs for withdrawal from treatment have 95% CIs that span unity, indicating that we have no conclu-
sive evidence that patients were more likely to withdraw from using the combined regimen than from using the control intervention. Comparing the withdrawal rates due to adverse effects of treatment, we again found that the 95% CIs for the RRs crossed unity, indicating that patients were no more likely to withdraw from using the combined regimen than from using the control intervention. Despite this, indirect comparisons suggest that use of acitretin is most likely to cause withdrawal, whereas UV-B phototherapy is least likely.

ADVERSE EFFECTS

There were no significant differences in the proportion of patients experiencing adverse effects between the combined regimens and their corresponding control interventions (Table 2). In addition, the pooled RRs for cutaneous and noncutaneous adverse effects all had 95% CIs that crossed unity, indicating that patients were no more likely to experience such effects from the addition of calcipotriene. However, results of the trials evaluated suggest that acitretin was almost 3 times more likely to cause adverse effects during the randomized treatment than PUVA therapy, which was associated with the lowest proportion of patients reporting adverse effects.

Overall, the addition of calcipotriene to several systemic treatments (acitretin, cyclosporine, and PUVA) may produce a small additive therapeutic effect in severe psoriasis without an increase in the incidence of short-term adverse effects. However, the results of patient assessment suggest that the magnitude of the effect observed is neither statistically nor clinically meaningful. In other words, a decrease in psoriasis severity, reflected in percentage change in PASI, may not be sufficient for the patient to classify the change as a categorical change, eg, from moderate to marked improvement in response RR as an outcome measure. Although the review does not exclude the possibility of small effects in favor of calcipotriene and UV-B combinations, there is also insufficient evidence to support the claim that topical calcipotriene enhances the effect of UV-B.

**IMPLICATIONS OF RESULTS**

Theoretically, any treatment that improves the therapeutic outcome (eg, time or likelihood of clearance) while minimizing the risks of toxic effects would be advantageous. Mostly on the basis of the results of single multicenter studies, topical calcipotriene has not been shown to substan-

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**Figure 3.** Mean rate ratios for cleared psoriasis between treatment groups by investigator overall assessment. Includes the trial, number of patients receiving combination/control treatment, and treatment duration. CPT indicates calcipotriene; PUVA, psoralen–UV-A. Error bars represent 95% confidence intervals.

**Figure 4.** Mean rate ratios for cleared psoriasis between treatment groups by patient overall assessment. Includes the trial, number of patients receiving combination/control treatment, and treatment duration. CPT indicates calcipotriene; PUVA, psoralen–UV-A. Error bars represent 95% confidence intervals.
tially enhance the effect of systemic therapy. There were relatively few studies, and it is possible that we could have missed small additive effects of calcipotriene, but the magnitude of the effect observed suggests that the response is not clinically relevant to the patient. A recent review concluded that calcipotriene and UV-B combinations were more effective than UV-B alone. This conclusion cannot be verified by our results. The former review included nonrandomized studies, and the results of primary studies were reported only as significant or not significant, with no attempt made to measure effect sizes or to pool results.

There was no increase in the incidence of withdrawal rates or adverse effects from combined treatment. Given that the adverse effects associated with systemic therapies are mostly dose dependent, the short duration of these RCTs is unlikely to detect the most critical adverse effects of treatment. Longer trials are needed to establish whether use of topical calcipotriene improves the risk-benefit ratio by reducing the long-term risks of toxic effects. Is there a dose-sparing effect? It seems that combination therapy can decrease the cumulative exposure to systemic therapy. Results of recent studies suggest that use of calcipotriene can reduce the number of UV-B exposures and the cumulative energy density. Other studies have shown significant reductions in the cumulative exposure to UV-A and acitretin. As yet, the clinical relevance of the amount of energy density saved has not been determined; however, from a theoretical point of view, less UV exposure is likely to cause fewer UV-related adverse effects. Likewise, lowering the daily dose of systemic drugs would be likely to result in a reduction in their dose-dependent adverse effects. This could also result in considerable savings in time and total costs.

Does use of topical calcipotriene prolong the duration of remission? The studies were not numerous enough for this analysis; only 4 trials reported relapse rates during posttreatment follow-up. Each trial used different relapse criteria and varied lengths of posttreatment follow-up. Because psoriasis is a chronic disease for most patients, differences in remission time after treatment might be a more important measure of a treatment’s relative efficacy than differences in the clearing capacity. We already proposed that the time to relapse would be a useful outcome measure, but the definition of relapse would need to be precisely defined and universally agreed on so that the results of different trials could be compared directly.

Other topical agents besides calcipotriene have also been shown to be effective adjuvant therapies in severe psoriasis. In practice, coal tar and topical corticosteroids are routinely used with many systemic therapies. Traditionally, coal tar has been used in combination with UV-B phototherapy in the Goekerman regimen. In recent years, anthralin, tacalcitol, and tazarotene have been reported to improve the outcome of second-line treatments, and their risk-benefit profile should be compared with that of calcipotriene.

**LIMITATIONS OF STUDY**

Publication bias is a potential threat to the validity of any systematic review. Although strenuous efforts were made to locate all RCTs, many of our conclusions were drawn from single studies. Two recent trials addressing the combined use of topical calcipotriene and UV-B phototherapy were excluded because they reported on nonrelevant outcomes for this study. A further 5 trials were excluded because of lack of randomization. Similar qualitative results were obtained in these trials, which gave us some confidence about the robustness of our conclusions. Moreover, not all the trials reported the outcomes of interest. Therefore, to obtain the pooled estimates, the trials included in the different analyses do not necessarily match. In particular, we were unable to extract data on withdrawal rates from 5 trials that conducted bilateral (right/left) comparisons.

There is no accepted definition of what constitutes meaningful clinical improvement in psoriasis. The PASI was selected as an outcome measure in this analysis for several reasons. First, it was the most commonly used outcome measure in the trials. Second, most trials collected data on a variety of outcomes, and as such there is the potential for bias due to the selective publication of results showing impressive treatment effects. Because we obtained PASIs for all but 2 of the included trials, the likelihood of bias due to selective publication of outcomes is minimal. However, we acknowledge that the PASI has sev-
general major problems and recognize that the results must be interpreted with caution.20

**CONCLUSIONS**

Evidence for some superiority of combination treatment over systemic treatment alone was obtained. The acitretin, cyclosporine, and PUVA treatment combinations showed statistical significance in the difference in PASI from baseline. However, this is not translated into an increase in the number of patients who achieve marked improvement or clearance. It has been suggested that topical administration of calcipotriene enhances the effect of UV-B phototherapy.19 In studies that met our inclusion criteria, a beneficial effect greater than that of UV-B irradiation alone was not detected.

In practice, cumulative exposure to systemic agents is substantial, increasing the lifetime risk of serious toxic effects. There is some evidence that topical calcipotriene therapy can reduce cumulative exposure to systemic treatments and thereby potentially lower the risks of toxic effects. The combination treatments did not result in aggravation or increased frequencies of short-term adverse effects. However, much longer clinical trials are warranted to identify the long-term efficacy and safety profile of the various combination therapies.

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From the Department of Medicines Management, Keele University, Keele (Dr Ashcroft); the Centre for Evidence-Based Pharmacotherapy, School of Life and Health Sciences, Aston University, Birmingham (Prof Li Wan Po); the Department of Dermatology, Queen’s Medical Centre, Nottingham (Prof Williams); and the Dermatology Centre, University of Manchester, Hope Hospital, Salford (Prof Griffiths), England. Dr Ashcroft has received funding from E. Merck Pharmaceuticals, which initially marketed tacalcitol in the United Kingdom. Prof Li Wan Po has received funding for studentships from E. Merck Pharmaceuticals and Leo Pharmaceuticals, manufacturers of calcipotriene. Prof Griffiths’ institution has been the beneficiary of research grants from Leo Pharmaceuticals and E. Merck Pharmaceuticals.

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The views expressed in this article are the personal views of the authors.

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**REFERENCES**


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<th>Total</th>
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<td>Crude rate</td>
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<td>20/121 vs 20/121</td>
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<td>NR</td>
<td>NR</td>
<td>1 (0.16-6.42)</td>
<td>1 (0.57-1.76)</td>
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<td>NR</td>
<td>NR</td>
<td>0 (-0.19 to 0.19)</td>
<td>0 (-0.09 to 0.09)</td>
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</table>

| Calcipotriene + UV-B (3×/wk) vs Placebo + UV-B (3×/wk) |
| Crude rate | 0/10 vs 0/10 | NR | NR | NR | NR |
| RR | 0.02 (-0.14 to 0.10) | NR | NR | NR | NR |
| RD | 0.04 (-0.09 to 0.01) | NR | NR | NR | NR |

| Calcipotriene + PUVA vs Placebo + PUVA |
| Crude rate | 12/77 vs 15/76 | 1/77 vs 4/76 | 19/64 vs 19/63 | 5/64 vs 0/63 |
| Weighted RR | 0.97 (0.41-1.84) | 0.42 (0.08-2.29) | 0.98 (0.59-1.63) | 4.59 (0.46-45.63) |
| Weighted RD | -0.03 (-0.14 to 0.08) | -0.04 (-0.10 to 0.03) | 0 (-0.13 to 0.12) | -0.07 (-0.001 to 0.15) |

| Calcipotriene + Acitretin vs Placebo + Acitretin |
| Crude rate | 16/76 vs 21/59 | 9/76 vs 13/59 | 74/76 vs 56/59 | 62/76 vs 45/59 |
| RR | 0.59 (0.34-1.03) | 0.54 (0.25-1.17) | 1.03 (0.96-1.10) | 1.07 (0.90-1.28) |
| RD | -0.15 (-0.30 to 0.01) | -0.10 (-0.23 to 0.03) | 0.02 (-0.04 to 0.09) | 0.05 (-0.09 to 0.19) |

| Calcipotriene + Cyclosporine vs Placebo + Cyclosporine |
| Crude rate | 9/76 vs 3/34 | 1/35 vs 2/34 | 18/35 vs 19/34 | 13/35 vs 9/34 | 17/35 vs 16/34 |
| RR | 0.49 (0.05-5.11) | 0.92 (0.59-1.43) | 1.40 (0.69-2.85) | 1.03 (0.63-1.69) |
| RD | -0.03 (-0.13 to 0.07) | -0.04 (-0.28 to 0.19) | 0.11 (-0.11 to 0.32) | 0.02 (-0.22 to 0.25) |

* NR indicates not reported; RR, rate ratio; RD, rate (risk) difference; and PUVA, psoralen–UV-A.


**Editor’s Comment**

F or information on evaluating systematic reviews, please see: Oxman AD, Cook DJ, Guyatt GH, for the Evidence-Based Working Group. Users’ guides to the medical literature, VI: how to use an overview. JAMA. 1994;272:1367-1371; and Greenhalgh T. How to read a paper: papers that summarise other papers (systematic reviews and meta-analyses). BMJ. 1997;315: 672-675. Available at: http://www.bmj.com/cgi/content/full/315/7109/672. Accessibility verified October 17, 2000.

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