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A long-term multicentre assessment of the safety and tolerability of calcitriol ointment in the treatment of chronic plaque psoriasis

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Summary

Calcitriol (1α,25-dihydroxyvitamin D₃), applied topically in an ointment base, has been shown to be effective in the treatment of chronic plaque psoriasis. This open study was designed to assess the safety and tolerability of 3 μg/g calcitriol ointment applied twice daily over treatment periods of up to 78 weeks. In the 253 evaluable patients with chronic plaque psoriasis no clinically relevant changes were observed in the baseline/end-point analyses of mean serum levels of total calcium, albumin-adjusted total calcium, phosphorus and creatinine, and plasma calcitriol levels. Mean values of 24-h urinary calcium, phosphorus, creatinine and hydroxyproline excretions, creatinine clearance and mean urinary calcium/creatinine ratio also did not show clinically relevant changes in the baseline/end-point analyses. The treatment was well tolerated, with no serious adverse events occurring during the course of the study. Eight patients withdrew from the study due to adverse events which, although not serious, were thought to be treatment-related: in seven patients skin irritation reactions and in one case a transient asymptomatic slight hypercalcaemia was observed. In addition, assessments of global severity, global improvement and Psoriasis Area and Severity Index scores confirmed the therapeutic efficacy of twice daily 3 μg/g calcitriol ointment demonstrated in an earlier controlled study. In conclusion, this study demonstrated that twice daily application of 3 μg/g calcitriol ointment is safe and well-tolerated in the treatment of chronic plaque psoriasis.

calcitriol (1α,25-dihydroxyvitamin D₃), the endogenously produced, active form of vitamin D, is important not only in the regulation of calcium homeostasis but also in skin physiology and pathophysiology. Studies have shown that calcitriol can inhibit proliferation and induce terminal differentiation of epidermal cells in vitro and a specific receptor for calcitriol has been identified on human epidermal keratinocytes and dermal fibroblasts. Calcitriol also exerts effects on the immune system. These properties of calcitriol suggested that it might be useful for the clinical management of hyperproliferative skin disorders, and a number of recent clinical studies have confirmed that calcitriol, applied topically in an ointment base, is effective for the treatment of chronic plaque psoriasis. These studies have been relatively short-term, however, with active treatment of a maximum of 6 weeks, and longer studies are required to assess the safety and tolerability of calcitriol ointment as well as its efficacy in long-term treatment.

The aim of the study reported here was to assess the long-term safety, tolerability and efficacy of 3 μg/g calcitriol ointment, applied twice daily to skin lesions in patients with chronic plaque psoriasis.
Patients and methods

Two hundred and fifty-seven outpatients with chronic plaque psoriasis were enrolled in this open, long-term, multicentre study, designed to assess the safety, tolerability and efficacy of twice daily application of 3 \( \mu \text{g/g} \) calcitriol ointment. All patients gave their written informed consent to participate in the study which was conducted according to the principles established in the Declaration of Helsinki. Ethics committee approval was obtained in the 20 participating centres.

Patients were selected at a screening visit and were excluded from the study if they were suffering from other types of psoriasis; had received any systemic or intralesional phototherapy for psoriasis during the previous 2 months; had used topical psoriasis therapy, with the exception of emulsifying ointment and/or tar shampoos during the week before the start of therapy; were receiving any concomitant medication or were suffering from any diseases (including skin infections) which might interfere with the assessment of the efficacy, safety or tolerability of the study drugs. Patients were also excluded if they had known hypersensitivity to vitamin D or its analogues. Women of child-bearing potential had to have a pregnancy test to rule out pregnancy prior to enrolment in the study and every 3 months during treatment, and were required to be using an effective method of contraception for the duration of the study.

At a screening visit the general health of the patient was assessed and 1 week later at the baseline visit (day 1) patients were provided with \( 3 \mu \text{g/g} \) calcitriol ointment for twice daily application to all psoriatic lesions on the body, except those on the head. No occlusion was to be used, and the patients could wash off the ointment 8-12 h after application. A cut-off date was defined 18 months after the first visit meaning that not all patients received treatment for a full 18 months.

Laboratory assessments of parameters reflecting calcium and phosphorus homeostasis were performed at each visit. Creatinine clearance and urinary calcium/creatinine ratio were calculated. In addition, in one centre serum levels of parathyroid hormone (PTH) and 25-hydroxyvitamin D and urinary hydroxyproline excretion were also measured at baseline and endpoint. A full general health assessment was carried out at the final visit.

The primary efficacy variable was the overall global improvement rating. Changes in psoriatic lesions were scored on a six-point rating scale, at weeks 2, 4, 8, 13 up to maximally week 78 of treatment, always in comparison with baseline. In addition, the Psoriasis Area and Severity Index (PASI) was modified slightly (head not included) and scores were recorded at baseline and at each assessment visits. Pruritus and overall global severity of the treated lesions were also scored. At one centre skin biopsies were taken to investigate how and to what extent the inflammatory, proliferative and differentiative components of psoriasis were affected by calcitriol treatment. These have been reported elsewhere.

One of the objectives of this study was to assess the relapse rate in patients whose chronic plaque psoriasis had cleared or considerably improved with treatment. Patients reporting a relapse were asked to come to the clinic for assessment of the PASI score, pruritus and overall global severity. According to the protocol of the trial, only patients showing a relapse within 3 months could re-enter the study.

The non-parametric, two-sided Wilcoxon signed-rank test was used to compare baseline safety (laboratory and vital signs) data with the end-point data.

Results

Four of the 257 patients who entered the study had neither safety nor efficacy data after receiving study medication and were excluded from all analyses. Demographic data and disease details of the 253 evaluable

Table 1. Demographic data and disease characteristics of evaluable patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Males (( n = 155 )) mean ± SD</th>
<th>Females (( n = 98 )) mean ± SD</th>
<th>Total (( n = 253 )) mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.4 ± 12.4</td>
<td>41.5 ± 13.7</td>
<td>42.1 ± 12.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.7 ± 12.9</td>
<td>67.1 ± 14.4</td>
<td>76.0 ± 15.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176.4 ± 6.9</td>
<td>163.1 ± 7.5</td>
<td>171.3 ± 9.6</td>
</tr>
<tr>
<td>History of psoriasis (months)</td>
<td>197.8 ± 142.7</td>
<td>211.1 ± 136.9</td>
<td>202.9 ± 140.4</td>
</tr>
<tr>
<td>Total body surface area involved (%)</td>
<td>14.8 ± 15.3</td>
<td>12.7 ± 12.4</td>
<td>14.0 ± 14.2</td>
</tr>
</tbody>
</table>

\( n \), number of patients.  
SD, standard deviation.
patients are summarized in Table 1. A total of 219 patients were treated continuously for at least 3 months, 149 for at least 6 months, 75 patients for at least 12 months and 16 patients for at least 18 months.

Forty-six patients (18%) withdrew from the study prematurely because their psoriasis improved or cleared, seven (2.8%) withdrew due to local intolerance and one (0.4%) due to hypercalcaemia. One hundred and eight patients (42.7%) were withdrawn to lack of efficacy. However, included in this were patients who showed improvement during the first weeks or months of treatment but then showed no further improvement or some deterioration upon continued treatment. (This is not uncommon in long-term studies of this type.)

The actual amount of ointment applied was dependent on the size of the lesions and the thickness of the applied layer of ointment. Patients were asked to return all tubes at the end of the study. Of the 80 patients who returned all tubes dispensed, the mean quantity of ointment used was 6 g/day (range 1–24 g/day). Twenty-four patients (30% of those patients who returned all tubes) used more than 1000 g calcitriol ointment and eight (10%) more than 2000 g during their treatment period. Five patients (6%) used on average more than 15 g ointment daily, while 13 patients (16%) used more than 10 g daily.

No serious adverse events or deaths occurred during the course of the study. Fifteen per cent of patients experienced a transient skin irritation reaction at some time. These reactions were generally mild. Eight patients withdrew from the study due to adverse events which, though not serious, were thought to be related to the study medication. Seven of these were considered to be skin irritation reactions and one patient developed a transient, asymptomatic slight hypercalcaemia.

No statistically significant and clinically relevant changes were observed in the baseline/end-point analyses of any laboratory parameter. Blood biochemistry baseline/end-point analyses for calcium, albumin-adjusted calcium, phosphorus, creatinine, calcitriol, PTH and 25-hydroxyvitamin D are summarized in Table 2. The mean values of 24-h urinary calcium, phosphorus, creatinine and hydroxyproline excretion, urinary calcium/creatinine ratio and creatinine clearance did not show clinically relevant changes in the baseline/end-point analyses. The mean systolic/diastolic blood pressure and mean pulse rate also remained well within the normal range throughout the study and baseline/end-point analysis did not reveal any clinically relevant changes in these parameters.

Ninety-six (40.1%) patients showed definite or considerable improvement at end-point compared with baseline, and clearance of psoriasis was reported in 39 (16.3%) patients. Forty-six patients who showed clearing or considerable improvement of psoriasis were withdrawn from the study due to this outcome. Eleven (23%) of these patients relapsed within 3 months and subsequently re-entered the study. From the remaining group of 36 patients, a relapse after 3 months was reported in six patients, and they were subsequently also re-entered into the study (although this should be considered a protocol violation).

The number of patients with severe or very severe psoriasis fell from 120 (47.4%) at baseline to 54 (21.4%) at end-point, while the number with none or slight psoriasis increased from 19 (7.5%) to 98 (38.8%). Pruritus showed a significant improvement over the course of the study. At baseline, 4.3% of the patients complained of severe, distressing pruritus, which had fallen to 1.2% at the 3- and 12-month assessments. At the start of the study, only 17% of patients had no specific complaint of pruritus, but this had improved to 48.4% at the 3-month assessment and 38.7% at

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Baseline mean ± SD</th>
<th>End-point mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium—total (mmol/l)</td>
<td>247</td>
<td>2.353 ± 0.108</td>
<td>2.343 ± 0.112</td>
<td>0.5016</td>
</tr>
<tr>
<td>Calcium—total adjusted (mmol/l)</td>
<td>244</td>
<td>2.222 ± 0.112</td>
<td>2.216 ± 0.119</td>
<td>0.3795</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>238</td>
<td>1.137 ± 0.193</td>
<td>1.114 ± 0.203</td>
<td>0.4064</td>
</tr>
<tr>
<td>Calcitriol (pg/ml)</td>
<td>228</td>
<td>40.29 ± 15.62</td>
<td>42.12 ± 17.14</td>
<td>0.1042</td>
</tr>
<tr>
<td>25-hydroxyvitamin D3 (pg/ml)</td>
<td>26</td>
<td>134.69 ± 50.32</td>
<td>122.97 ± 56.11</td>
<td>0.1619</td>
</tr>
<tr>
<td>Parathyroid hormone (pmol/l)</td>
<td>31</td>
<td>0.312 ± 0.115</td>
<td>0.325 ± 0.120</td>
<td>0.5500</td>
</tr>
</tbody>
</table>

n, number of patients.
SD, standard deviation.
Discussion

Twice daily application of 3 μg/g calcitriol ointment for up to 78 weeks had no clinically relevant effects on calcium and phosphorus homeostasis and renal function in this large group of patients with chronic plaque psoriasis. These results confirm and extend the findings of previously reported short-term studies and they appear to refute suggestions that topical calcitriol treatment may be unsafe due to unwanted effects on systemic calcium homeostasis. For, even in patients who used large quantities of the ointment for many months, no noteworthy changes were seen in serum total calcium levels or urinary calcium excretion.

The treatment was generally very well tolerated and there were no reports of serious adverse events. It is an important advance of antipsoriatic therapy that vitamin D₃ analogues permit safe long-term management of psoriasis over many months, and a relapse was reported in a further six patients after 3 months. This relapse rate is considerably lower than that observed after topical corticosteroid therapy, and the possible mechanisms involved warrant further investigation.

In conclusion, this open study demonstrated that twice daily application of 3 μg/g calcitriol ointment is safe and well tolerated in the long-term treatment of chronic plaque psoriasis.

Acknowledgment

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Table 3. Psoriasis Area and Severity Index (PASI) score

<table>
<thead>
<tr>
<th>Assessment time</th>
<th>n</th>
<th>Absolute score</th>
<th>Percentage reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>253</td>
<td>9.71</td>
<td>—</td>
</tr>
<tr>
<td>3 months</td>
<td>253</td>
<td>4.24</td>
<td>53.24</td>
</tr>
<tr>
<td>12 months</td>
<td>180</td>
<td>4.23</td>
<td>54.28</td>
</tr>
<tr>
<td>18 months</td>
<td>253</td>
<td>4.08</td>
<td>59.59</td>
</tr>
<tr>
<td>End-point</td>
<td>253</td>
<td>4.32</td>
<td>51.24</td>
</tr>
</tbody>
</table>

n, number of patients.

end-point. The PASI score showed a marked improvement after 3 months treatment (53.2% reduction in score), which was maintained over the whole course of the study (see Table 3).

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