1% Pimecrolimus, 0.005% Calcipotriol, and 0.1% Betamethasone in the Treatment of Intertriginous Psoriasis

A Double-blind, Randomized Controlled Study

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Objective: During the last decades, management of intertriginous psoriasis (IP) has been unsatisfactory because of the adverse effects associated with long-term corticosteroid application and the lack of alternatives. Recently, both pimecrolimus and tacrolimus have been investigated for this indication and shown to be safe and effective. So far, to our knowledge, a comparison of one of these drugs with standard regimens for IP has not been performed.

Design: A single-center, 4-week, double-blind, randomized, vehicle-controlled comparison study to assess the safety and efficacy of 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone valerate in the treatment of IP.

Setting: Dermatologic hospital at Ruhr University of Bochum.

Patients: Eighty adults with IP.

Interventions: Treatment of IP with 1% pimecrolimus, 0.005% calcipotriol, 0.1% betamethasone, or the vehicle once daily for 28 days.

Main Outcome Measures: Mean reduction of the Modified Psoriasis Area and Severity Index (M-PASI) score after 28 days of treatment was considered the primary outcome measure, which was analyzed on an intention-to-treat basis. The secondary outcome was a visual analog scale score for itching.

Results: After 4 weeks of treatment, the 3 active compounds and the vehicle resulted in a significant decrease in mean M-PASI score (86.4% for 0.1% betamethasone, 62.4% for 0.005% calcipotriol, 39.7% for 1% pimecrolimus, and 21.1% for vehicle). The 0.1% betamethasone was significantly more effective than 1% pimecrolimus during the study period (P<.05). No significant difference was found between 0.005% calcipotriol and 0.1% betamethasone and between 0.005% calcipotriol and 1% pimecrolimus. The visual analog scale score for pruritus decreased by 78% for 0.1% betamethasone, 57% for 0.005% calcipotriol, 35% for 1% pimecrolimus, and 43% for the vehicle, again demonstrating a clear advantage for the corticosteroid (P<.05).

Conclusions: The 1% pimecrolimus was shown to be less potent than 0.1% betamethasone in the treatment of IP. Considering the adverse-effect profile of long-term application of corticosteroids, occasional or intermittent rescue therapy with short-term topical corticosteroids and maintenance with a less potent agent, such as 1% pimecrolimus or 0.005% calcipotriol, might be appropriate for patients with IP in general practice.

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PSORIASIS, AN INFLAMMATORY skin disease with genetic susceptibility and an immunologic origin, is a frequent reason for people to consult dermatologists. Plaque-type psoriasis represents the most common form, and topical treatment with corticosteroids and analogues of cholecalciferol (vitamin D3) (eg, calcipotriol or tacalcitol) is usually sufficient to clear lesions in most patients. In a subset of patients, psoriasis is located in the intertriginous areas, involving the axillae, submammary region, inguinal folds, buttocks, and genitals. Patients who exhibit intertriginous psoriasis (IP) often complain about intense itching, irritation from sweating, and soreness. These symptoms may have devastating psychological and emotional consequences.

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Management of IP usually includes the use of topical corticosteroids, but their long-term use is associated with well-known adverse effects (skin atrophy, tel-
Vehicle-controlled studies and shown to be safe and effective. 
Investigated for the treatment of IP in double-blind, vehicle-controlled studies and shown to be safe and effective. 
Recently, 1% pimecrolimus and 0.1% tacrolimus, both members of a new group of anti-inflammatory drugs, the calcineurin inhibitors, have been investigated for the treatment of IP in double-blind, vehicle-controlled studies and shown to be safe and effective. 
Calcineurin inhibitors, approved by the Food and Drug Administration for atopic dermatitis, selectively block T-lymphocyte and mast cell inflammatory cytokine production. 
As nonsteroids, they do not alter collagen synthesis and are thus an interesting treatment option for sensitive skin areas. 
Additionally, 1% pimecrolimus was reported to be equal to clobetasol-17-propionate (0.05%) in plaque-type psoriasis when applied under occlusion. 
So far, to our knowledge, a controlled study comparing the safety and efficacy of 1% pimecrolimus with topical standard drugs in IP has not been performed. We therefore initiated a double-blind, vehicle-controlled, single-center study of 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone valerate in the treatment of IP.

STUDY DESIGN

This study was a randomized controlled trial that compared 1% pimecrolimus, 0.005% calcipotriol, 0.1% betamethasone, and the vehicle in the treatment of IP with a 4-week treatment period and a 6-week follow-up without therapy. The setting was a university hospital (Department of Dermatology, Ruhr University of Bochum). All patients were informed about the study procedures and gave written informed consent. The study protocol was approved by the ethics review board of Ruhr University of Bochum.

PATIENTS

Patients were recruited from dermatologic outpatient clinics and were supplemented by patients who had not attended our clinic before but had heard or read about the trial. Patients were recruited from July 15, 2004, to January 31, 2005, and in total, 80 adult patients with the clinical diagnosis of IP were included. Patients at least 18 years of age with continuous IP for a minimum of 6 months but who were otherwise healthy were eligible for enrollment in the study. Therapies that led to exclusion were systemic corticosteroids, immunosuppressants, UV light (eg, UV-A, UV-B, and psoralen–UV-A in the previous 4 weeks), and topical treatment of the target lesions (in the previous 2 weeks). Other exclusion criteria comprised acute guttate or pustular psoriasis, pregnancy or lactation, severe concurrent infectious diseases, and diseases associated with immunosuppression or malignancy, drug dependency, mental dysfunction, or other factors that limited compliance with the study.

STUDY MEDICATION

Patients were randomized in a 3:1 ratio to receive a pimecrolimus cream–based regimen, a conventional control treatment (betamethasone or calcipotriol), or the vehicle for 4 weeks. Treatment was assigned by computer-generated randomization lists. Identical tubes identified only by randomization number were supplied by the hospital’s pharmacy. Study medication was to be used on affected areas once daily, and no concomitant topical treatment, including emollients, was allowed on IP lesions. Topical standard therapy for psoriasis on other areas of the body was allowed to be constantly maintained. During the follow-up period, no topical treatment for IP was allowed.

PRIMARY AND SECONDARY OUTCOME MEASURES

Clinical visits during the treatment and follow-up periods were performed at day 0 (baseline), day 14, day 28 (end of treatment), and follow-up (day 42 and day 70). Photographic documentation was performed at baseline, end of treatment, and end of follow-up. At each visit, assessment of efficacy was performed using the Modified Psoriasis Area and Severity Index (M-PASI), as previously described. In brief, the M-PASI is a modified area score in which the maximum of involved skin is considered to be 100%. Erythema, infiltration, and desquamation are each assigned a value from 0 to 4; the sum of these values is multiplied with a score for the involved area (Table 1). The mean reduction in the M-PASI score after 28 days of treatment was considered the primary outcome measure. Pruritus was evaluated at each clinical visit by means of a visual analog scale (VAS) score on a 10-point scale, with 0 as the absence and 10 as the maximum of pruritus (secondary outcome measure). Safety assessments consisted of monitoring and recording all adverse events by their severity and potential relationship to the study medication.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS statistical software, version 11.0 for Windows (SPSS Inc, Chicago, Ill). The null hypothesis was based on the assumption that there is no difference in efficacy among the preparations used in the present trial. The primary outcome was analyzed on an intention-to-treat (ITT) basis using baseline M-PASI score and last available M-PASI score of all randomized patients. Exploratory arm comparative analysis of ITT data was also assessed at other times, including day 14, day 42, and day 70. Analysis of data distribution was assessed by the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) for 4 independent samples was used for interarm ITT comparisons. Subsequently, the Tukey test for pairwise comparisons was used to determine which therapeutic regimen was significantly different from the others. Intra-arm analysis of ITT data was assessed by means of 2-sided paired t tests. Mean differences and standard deviations of differences were calculated. Statistical significance was set at P<.05 (2-sided).

Table 1. Modified Psoriasis Area and Severity Index (M-PASI) Scores*

<table>
<thead>
<tr>
<th>M-PASI Score</th>
<th>Erythema, Infiltration, and Desquamation</th>
<th>Involved Area, % of Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Slight</td>
<td>1-9</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>10-29</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>30-49</td>
</tr>
<tr>
<td>4</td>
<td>Very severe</td>
<td>50-69</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>70-89</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>90-100</td>
</tr>
</tbody>
</table>

*M-PASI = (Erythema Score + Infiltration Score + Desquamation Score) × Modified Area [range, 0-72].
RESULTS

A total of 80 patients were enrolled into the study, 20 patients in each of the 4 treatment arms. Of the 80 patients, 75 were included in the ITT analysis, and 5 patients withdrew from the study. A flow diagram of patient treatment, including the safety and ITT populations as well as reasons for discontinuation, is shown in Figure 1. Patient demographics and baseline characteristics of the safety population are listed in Table 2.

PRIMARY OUTCOME

From baseline to the end of treatment (day 28), mean M-PASI scores significantly decreased by 86.4% for 0.1% betamethasone, 62.4% for 0.005% calcipotriol, 39.7% for 1% pimecrolimus, and 21.1% for the vehicle, indicating a decrease in M-PASI score from 22.1 to 2.9 \( (P/\text{H11021}.001) \), 25.3 to 9.7 \( (P/\text{H11021}.001) \), 19.2 to 11.5 \( (P/\text{H11021}.001) \), and 18.2 to 13.8 \( (P/\text{H11021}.008) \), respectively. Post-ANOVA pairwise interarm comparisons by means of the Tukey test revealed that betamethasone was significantly more effective than both 1% pimecrolimus and the vehicle \( (P/\text{H11021}.01) \); however, no significant difference was found between 0.005% calcipotriol and 0.1% betamethasone and between 0.005% calcipotriol and 1% pimecrolimus. The 1% pimecrolimus did not show a significant advantage over the vehicle. Further results of the M-PASI scoring are shown in Figure 2. During the follow-up period (day 42), the M-PASI score slightly increased in each of the 3 treatment arms. This increase was less pronounced for 1% pimecrolimus (M-PASI score results from day 28 to days 42 and 70: 11.45 vs 12.53 vs 12.75). Nevertheless, 0.1% betamethasone was still significantly better than 1% pimecrolimus during the fol-
low-up period (day 28, \(P < .05\)). At the end of the follow-up period (day 70), no significant differences among the 4 study arms were observed (M-PASI score results from day 28 to days 42 and 70, respectively: 1% pimecrolimus, 11.45 vs 12.53 vs 12.75; 0.1% betamethasone, 2.94 vs 6.79 vs 9.65; 0.005% calcipotriol, 9.68 vs 16.11 vs 17.63; vehicle, 13.84 vs 16.42 vs 14.63).

SECONDARY OUTCOME

Regarding improvement of pruritus by means of VAS scoring, 0.1% betamethasone also proved to be more effective than 0.005% calcipotriol, 1% pimecrolimus, and the vehicle. This advantage was significant in post-ANOVA pairwise interarm comparisons by means of the Tukey test (betamethasone vs pimecrolimus and vehicle, \(P < .05\)). Pimecrolimus was less effective than the other substances, including the vehicle. However, these differences were not significant. The VAS score of pruritus decreased by 78% for 0.1% betamethasone, 57% for 0.005% calcipotriol, 35% for 1% pimecrolimus, and 43% for the vehicle, indicating a decrease in the score from 5.5 to 1.2 (\(P < .001\)), 4.8 to 2.0 (\(P < .001\)), 4.3 to 2.8 (\(P = .03\)), and 4.5 to 2.6 (\(P = .004\)), respectively. Further results of the VAS scoring are shown in Figure 3.

TOLERABILITY

Serious adverse events did not occur during the study. However, 5 patients treated with 1% pimecrolimus cream reported an increase in itching and burning shortly after application. This transient increase in itching occurred during the first 2 weeks of the study within 30 minutes after application and decreased despite continuing therapy. After day 14, none of the patients treated with 1% pimecrolimus cream reported persisting itching or burning after application. Two patients treated with 0.005% calcipotriol reported an increase in erythema, warmth, and irritation after application of the study medication. No further action was taken because of clearance of these symptoms within the first 2 weeks of treatment. One patient treated with the vehicle experienced herpes genitalis within the follow-up interval. No adverse events were seen in the 0.1% betamethasone group.

**COMMENT**

Within the last decades, treatment of IP was mainly restricted to the use of middle- to high-potency topical corticosteroids worldwide. Because long-term application of corticosteroids is associated with a well-known profile of adverse effects, especially in areas with increased percutaneous absorption such as the inguinal folds and genital skin, new therapeutic alternatives are mandatory. Recently, a double-blind, randomized, vehicle-controlled study in 57 patients with IP was performed and demonstrated the efficacy of 1% pimecrolimus for this indication. After 8 weeks of treatment, 71.4% of patients treated with 1% pimecrolimus revealed a substantial clinical improvement, resulting in an Investigator’s Global Assessment score of 0 compared with only 20.7% for those treated with the vehicle. However, a direct comparison with a topical corticosteroid control group was not performed in that study. Furthermore, it lacked a follow-up period.

The present trial is the first attempt, to our knowledge, to evaluate and compare the effects of 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in a controlled setting. At the end of treatment (day 28),
the primary analysis time point, all 3 active compounds showed a substantial clinical improvement demonstrated by a significant decrease in mean M-PASI score (Figure 4). In the vehicle group, a less pronounced but still significant improvement reflected by a decreased M-PASI score and clear reduction in pruritus by means of VAS scoring were observed. These results may not be explained by a placebo effect alone but underline the known beneficial effects of emollients in the treatment of psoriasis through increased hydration of the stratum corneum and keratolytic effects. However, 0.1% betamethasone resulted in a significantly better clinical outcome compared with 1% pimecrolimus. This finding is in contrast to a study performed by Mrowietz et al, in which 1% pimecrolimus was equally effective to 0.05% clobetasol-17-propionate when applied to plaque-type psoriasis under occlusion performed with Finn chambers. This discrepancy can be explained in part by the missing enhanced occlusion in our trial. Furthermore, we cannot exclude the possibility that our treatment interval of 28 days was not long enough for pimecrolimus to completely establish its beneficial effects. Gribetz et al, who observed significantly better results (71% had an Investigator’s Global Assessment score of 0 or 1 after 8 weeks of therapy) in the treatment of IP with pimecrolimus, chose a longer mean ± SD treatment period of 58 ± 12 days. The course of amelioration under pimecrolimus shown in Figure 2 suggests that a longer treatment regimen might lead to an adjustment in the curve runs of pimecrolimus and betamethasone; with beta-
methasone a rapid plunge in the curve is observed within the first 2 weeks of treatment, whereas with pimecrolimus a more gradual but less pronounced reduction in M-PASI score is observed. Nevertheless, the clinical outcome of 0.1% betamethasone was significantly better than that of 1% pimecrolimus during the complete follow-up period. Finally, the patient number of 20 per group was relatively low, and hence the study was powered to detect only large differences.

Cholecalciferol (vitamin D₃) analogues such as calcipotriol are well known to induce skin irritations; therefore, their use for the inguinal folds and genitals has been recommended with care.²¹⁻¹⁰ However, calcipotriol was well tolerated in this study, with only mild irritation and erythema in 2 patients. So far, only 1 uncontrolled trial has been reported to examine the effectiveness of calcipotriol in IP.¹ In that study, 12 patients were treated with calcipotriol for 6 weeks, resulting in a decrease in M-PASI score from 31.7 to 19.7. This observation is similar to the results of our study. Unfortunately, the authors did not report on the follow-up and posttreatment skin status of these patients.

Calcineurin inhibitors are known to cause burning or itching, especially when the skin barrier is compromised. Consecutively, 25% of patients treated with pimecrolimus reported an increase in itching and burning shortly after application in the present trial. Pimecrolimus was disappointing in this regard when compared with betamethasone (no adverse effects) and calcipotriol (erythema, warmth, and irritation in 2 patients). However, most reactions lasted less than 30 minutes and resolved after a few days.

In conclusion, this study indicated the efficacy of all 3 active compounds, 1% pimecrolimus, 0.1% betamethasone, and 0.005% calcipotriol (as well as the vehicle) in the treatment of IP. The 0.1% betamethasone was clearly more effective than 1% pimecrolimus, confirming that treatment with corticosteroids is still the most effective topical approach for psoriasis. However, their use in long-term management, particularly for the treatment of intertriginous areas, which are more prone to steroid adverse effects, is limited. To combine the rapid anti-inflammatory effects of a topical corticosteroid with the favorable long-term effects and safety profile of pimecrolimus or calcipotriol, short-term application of topical corticosteroids for acute disease followed by maintenance treatment with one of these agents seems to be a reasonable approach in the treatment of IP. Future studies are warranted to further evaluate the effects of calcineurin inhibitors in the long-term use of IP and to directly compare pimecrolimus and tacrolimus for this indication.

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REFERENCES