Effectiveness of the Ascomycin Macrolactam SDZ ASM 981 in the Topical Treatment of Atopic Dermatitis

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Objective: To compare the safety and efficacy of 1% SDZ ASM 981 cream and a matching placebo cream in the treatment of patients with moderate atopic dermatitis.

Design: A randomized, double-blind, placebo-controlled, right-and-left comparison study.

Setting: Academic referral center.

Patients: Thirty-four adult patients with moderate atopic dermatitis.

Intervention: Topical 1% SDZ ASM 981 cream was applied twice daily (n = 16) or once daily (n = 18) and compared with a corresponding placebo cream base.

Main Outcome Measures: Efficacy was measured using a 4-point (0-3) scale for erythema, pruritus, exudation, excoriation, and lichenification (Atopic Dermatitis Severity Index [ADSI]). The ADSI score was defined as the sum of these 5 ratings (range, 0-15) and was determined on the pretreatment day (1 to 14 days before day 0) and on days 0, 2, 4, 7, 9, 11, 14, 16, 18, and 21. The percentage change from baseline (day 0) in the ADSI score was calculated on each of these days. Safety was evaluated by monitoring of adverse events, physical examination, hematologic examination, clinical chemistry studies, urinalysis, and measurement of blood levels of SDZ ASM 981.

Results: Of the 38 patients recruited, 34 started and 28 completed treatment according to the protocol. Sixteen patients used the cream twice daily, with significant improvement after 2 days of treatment. Within 3 weeks of topical therapy with 1% SDZ ASM 981 cream twice daily, a mean reduction of 71.9% in the ADSI score was observed at the actively treated test sites compared with a mean reduction of 10.3% at the placebo-treated test sites (P<.001). Efficacy was significantly less in the group treated once daily (n = 18), with mean reductions of 37.7% and 6.2%, respectively. The efficacy was especially apparent for pruritus and excoriation. There were no clinically relevant drug-related adverse effects.

Conclusions: Treatment with 1% SDZ ASM 981 cream was well tolerated. Twice-daily application of 1% SDZ ASM 981 cream was significantly more effective than use of the corresponding placebo and more effective than once-daily treatment. The new macrolactam ascomycin derivative SDZ ASM 981 is a promising agent for the treatment of patients with atopic dermatitis. More elaborate phase 2 and 3 trials are under way to fully investigate the potential of this medication.

Arch Dermatol. 1998;134:805-809

A topic dermatitis (AD) is one of the most common skin diseases, with a complex genetic background,1 a lifetime prevalence of up to 20%,2,3 and an increasing number of cases.4-6 Although there are other treatments (emollients, phototherapy, elimination of exacerbating factors, psychotherapy, and patient education), the number of medications for treating this chronic disease is limited: tar preparations, topical corticosteroids (low, medium, and high potency), antiseptics, antibiotics, cyclosporine, and antihistamines.7 Most treatments may be used only for a limited period or are less effective in the long term (tachyphylaxis). The development of new compounds is mandatory for treatment of this persistent disease.

In view of the emphasis on the immunopathogenesis of AD,8 new immunosuppressive compounds are being investigated. Systemic use of cyclosporine has been proven to be effective,10-12 but its use is restricted to severe cases only. Topical application of cyclosporine is not effective,13 in contrast to the cyclic macrolide tacrolimus (FK 506), which proved to be effective in treating patients with AD.14,15 Results of studies of the topical treatment of allergic contact dermatitis in pigs with other cytokine-inhibiting, anti-inflammatory drugs, such as the ascomycin derivative (SDZ ASM 981), indicated that they might be effective in the topical treatment of skin disease in man.16,17 Clearing of psoriatic lesions has been reported after topical application of 1% SDZ ASM 981 ointment under occlusion for 14 days (U. Mrowietz, et al, unpublished data, 1995).
PATIENTS AND METHODS

PATIENT POPULATION

Patients with AD were recruited from an academic dermatology outpatient clinic (n = 20) and were supplemented by patients who had not attended our clinic before but had heard or read about the trial (n = 18). All patients had AD according to the criteria of Hanifin and Rajka, with at least 1% of the body surface area affected on both arms. For assessment of severity of the dermatitis we used the Atopic Dermatitis Severity Index (ADSI). This index (range, 0-15) consists of the sum of the scores for pruritus, erythema, excoriation, and lichenification, all scored on a 4-point (range, 0-3) scale. The ADSI score had to be at least 6, and the severity of the 2 sides was not allowed to differ by more than 1 point. In addition, the 2 sides had to be symmetrical.

Exclusion criteria were as follows: patients receiving radiation therapy, systemic therapy with cytostatics, or immunosuppressive drugs within 24 weeks before randomization, receiving phototherapy or systemic therapy for AD within 1 month before randomization; receiving antibiotics or topical therapy for AD within 2 weeks before randomization (however, the once-daily use of 1% hydrocortisone acetate was allowed on all lesions with the exception of the test sides selected for the study, and emollients were allowed to be used liberally but not on the test sides); taking antihistamines within 1 week before randomization; and acute skin infection (superinfection) at randomization.

All patients were informed of study procedures and gave written informed consent. The study protocol was approved by the local medical ethics committee.

EVALUATION OF PATIENTS

Clinical evaluations included a medical history, a drug history, current medications, and adverse effects. At pretreatment (1-14 days before day 0) and on days 0, 4, 11, and 21, physical examination (including blood pressure and pulse rate measurements), hematologic examination, clinical chemistry studies, and urinalysis were performed. On days 0 and 4, 3 samples per visit were taken to monitor the blood levels of SDZ ASM 981: before and 2 and 6 hours after the morning application of study medication. On days 11 and 21, 1 sample per visit was taken to monitor the blood levels of SDZ ASM 981.

The clinical evaluations were all performed by the same blinded investigator (E.J.M.V.), and the blood samples were taken by the staff of an outpatient clinic laboratory.

CRITERIA FOR RESPONSE (ADSI SCORE AND PARTIAL AND COMPLETE CLEARANCE)

At all visits, 5 symptoms of AD (pruritus, erythema, excoration, excoriation, and lichenification) were scored on a 4-point (range, 0-3) scale. The sum of the 5 symptoms was defined as the ADSI score (range, 0-15), a modification of the standardized grading according to Hanifin. Scoring was performed separately for the 2 treated areas.

TREATMENT REGIMEN

The study was designed as a double-blind, randomized, placebo-controlled trial with the use of topical 1% SDZ ASM 981 cream vs placebo cream (cream base) for 21 days on 2 comparative target areas (minimum 1% and maximum 2% of the total body surface area per target area), with one site on the left arm and one site on the right arm. Most patients used the study medication on the left and right elbow folds.

On days 0 and 14, the patients received 2 identical 30-g tubes marked “left” and “right.” The time of application was noted on a diary card, which was checked at every visit.

Sixteen patients were randomized to twice-daily application (with a recommended 12-hour interval), and 18 patients were randomized to once-daily application (every day at the same time).

STATISTICAL ANALYSIS

All analyses were performed using the “intention-to-treat” principle. At the end of treatment, P values based on the matched-paired, signed rank sum test were displayed to formally test for any difference in treatment effect. This analysis was repeated at the other times to aid data interpretation. Scores for each of the 5 components of the ADSI were tabulated separately in a series of contingency tables. For each visit after baseline, the percentage change from baseline in the ADSI score was calculated. The time until partial clearance (0<ADSI≤2) and complete clearance (ADSI = 0) was analyzed using descriptive statistics and within-patient survival techniques.

Table 1. Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Twice-Daily Group</th>
<th>Once-Daily Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. recruited</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>No. randomized</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>No. with intention to treat</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>No. who completed the study</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Male/female, No.</td>
<td>9.7</td>
<td>7.11</td>
</tr>
<tr>
<td>Mean (SD) age, y</td>
<td>35.75 (13.65)</td>
<td>29.11 (13.21)</td>
</tr>
<tr>
<td>Mean (SD) ADSI* score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>side treated with SDZ ASM 981</td>
<td>8.06 (1.39)</td>
<td>7.72 (1.23)</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.13 (1.20)</td>
<td>7.78 (1.26)</td>
</tr>
</tbody>
</table>

*ADSI indicates Atopic Dermatitis Severity Index.

SDZ ASM 981 is a cytokine inhibitor. It inhibits activation of T cells by inhibiting T-cell proliferation and antigen-specific activation. The transcription and release of both Th1-type and Th2-type cytokines from human T cells are inhibited. Mast cells are inhibited by suppression of the release of proinflammatory mediators from granules and transcription of the late-phase cytokine tumor necrosis factor α. With a molecular weight of 810 kD, SDZ ASM 981 probably does not pass the normal skin barrier. Because of the defective skin barrier of atopic patients, we reasoned that this drug may transfer through the atopic skin and be effective against the dermatitis.

To investigate this hypothesis, we studied the ascomycin derivative SDZ ASM 981 in a double-blind, placebo-controlled, right-and-left comparison, proof-of-concept study of 34 adult patients with AD.
RESULTS

PARTICIPANTS

Between April 25, 1996, and October 1, 1996, 38 patients were recruited. Three patients withdrew consent and 1 patient was excluded because of a skin infection before treatment (this infection started between the pretreatment visit and the day 0 visit). The remaining 34 patients were randomized and treated according to the protocol. The baseline characteristics are shown in Table 1.

After randomization, 7 patients discontinued participation during the treatment phase. The main reason (n = 4) was exacerbation of the AD on untreated or placebo-treated sides. The other 3 patients discontinued participation because of a skin infection on the placebo-treated side (n = 1), failure to return for scheduled visits (n = 1), or “other reasons” (n = 1).

ANALYSIS

For patients treated twice daily (n = 16), significant improvement was already observed after 2 days of treatment. On day 4, there were mean ADSI score reductions of 41.3% on the SDZ ASM 981–treated side and 1.2% on the placebo-treated side (P < .001). Within 3 weeks of therapy with 1% SDZ ASM 981 cream, a mean reduction of 71.9% in the ADSI score was observed at the actively treated test sites compared with a mean reduction of 10.3% at the placebo-treated test sites (P < .001) (Table 2 and Figure 1). The median time to partial clearance (0 ≤ ADSI ≤ 2) for the actively treated test sites was 8 days. By the end of treatment, 12 of 16 patients reached partial clearance and 3 patients were totally cleared (ADSI = 0) on the actively treated test sides (Table 3).

For patients treated once daily (n = 18), efficacy was less with mean reductions of 37.7% on the actively treated sides.
side and 6.2% on the placebo-treated side (Figure 2). None of the patients had total clearance at study end. Only 3 of 18 patients had partial clearance (Table 3). The efficacy was especially apparent for pruritus and excoriation (Table 4). Only a few patients displayed signs of exudation.

SAFETY

Adverse Events

In this study, no skin irritation or any other local adverse effects were observed. No relevant changes were observed in the patients’ laboratory test values (hematologic examination, clinical chemistry studies, and urinalysis). All vital signs and results of physical examinations were normal. There were no clinically significant adverse effects (ie, drug-related adverse events).

Pharmacokinetics

Only 2 of 121 samples from the 16 patients treated twice daily were above the limit of quantification (0.1 ng/mL) of the radioimmunoassay for the measurement of SDZ ASM 981 concentrations in whole blood. One sample with a concentration of 2.39 ng/mL was taken at day 0, 2 hours after the first application of study medication. The other sample, which was taken from another patient, had a level of 0.22 ng/mL on day 11, 6 hours after the last application of medication.

COMMENT

This is the first study using SDZ ASM 981 in patients with AD. The 1% SDZ ASM 981 cream was significantly more effective than the placebo cream base. The twice-daily application with SDZ ASM 981 presented a remarkable improvement in the first 9 days, followed by status quo during the next 12 days, as shown in Figure 1. However, this observation reflected more the limitation of the scoring system used in this study than the clinical improvement of the patients. In particular, the erythema score remained 1 (mild) even when the area of the erythema was getting smaller. In addition, improvement of lichenification was slowly following the improvement of the other clinical improvement.

We expected a worsening of the AD on the placebo-treated sides. Instead, the mean results showed an improvement on the placebo-treated sides, as shown in Figures 1 and 2. An explanation of this could be that some patients used the frequent visits to our outpatient clinic to also visit the psychologist to help alleviate their stress or scratch behavior. In addition, the intensive patient-physician interaction may have improved overall compliance, enhancing the placebo effect. Finally, the cream emollient characteristics of the base may have given some improvement of the AD.

The 1% SDZ ASM 981 cream applied on 1% to 2% of the body surface area was well tolerated and safe in this study. There were no, or only low, levels of SDZ ASM 981 found in the blood samples. Two samples containing a level above the limit of quantification (0.1 ng/mL) are most likely
the result of contamination of the blood sample during blood draw. This is further explained by the following: the elbow is the standard area for a venipuncture in our hospital, and most patients used the cream on the elbow fold. From studies about the absorption of molecules with a comparable molecular weight to SDZ ASM 981, we know that the highest blood levels were reached between 3 and 6 hours after application and that blood levels decreased as the clinical symptoms improved. Furthermore, the detectable blood levels appeared on days 1 and 12 in 2 isolated samples from 2 independent patients, and contamination remains the most likely explanation.

Twice-daily treatment was more effective than once-daily treatment. The reduction of the ADSI score and the number of partial or total clearances were greater in the group treated twice daily.

The patients recruited from our dermatology outpatient clinic returned after the study for their usual visits outside the study protocol. After completing treatment with SDZ ASM 981 cream, the AD recurred gradually, without a rapid rebound after discontinuing use of the study medication.

In conclusion, the new macrolactam ascomycin derivative SDZ ASM 981 is a promising agent for the treatment of patients with AD. More elaborate phase 2 and 3 trials are under way to fully investigate its potential.

Accepted for publication March 21, 1998.

The study was funded by Novartis Pharma AG, Basel, Switzerland.

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Table 4. Summary Statistics at Baseline and at End of Study*

<table>
<thead>
<tr>
<th></th>
<th>Twice-Daily Group (n = 16)</th>
<th>Once-Daily Group (n = 18)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of Study</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDZ ASM 981</td>
<td>2.31 (0.60)</td>
<td>0.38 (0.62)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.31 (0.60)</td>
<td>1.56 (0.96)</td>
</tr>
<tr>
<td>Exudation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDZ ASM 981</td>
<td>1.75 (0.45)</td>
<td>0.69 (0.60)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.81 (0.40)</td>
<td>1.88 (0.62)</td>
</tr>
<tr>
<td>Excoriation</td>
<td></td>
<td></td>
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<tr>
<td>SDZ ASM 981</td>
<td>0.06 (0.24)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.06 (0.25)</td>
<td>0.19 (0.54)</td>
</tr>
<tr>
<td>Lichenification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDZ ASM 981</td>
<td>2.00 (0.73)</td>
<td>0.38 (0.50)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.00 (0.63)</td>
<td>1.75 (0.93)</td>
</tr>
<tr>
<td>Atopic Dermatitis Severity Index score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDZ ASM 981</td>
<td>1.94 (0.57)</td>
<td>0.88 (0.62)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.94 (0.57)</td>
<td>1.94 (0.77)</td>
</tr>
</tbody>
</table>

* Values are expressed as mean (SD).

REFERENCES


