Development of new treatment modalities for atopic dermatitis
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Low systemic exposure after repeated topical application of pimecrolimus (Elidel®, SDZ ASM 981) in patients with atopic dermatitis

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Chapter 5

SUMMARY

Context: SDZ ASM 981 is a selective inhibitor of inflammatory cytokine release developed specifically for the treatment of inflammatory skin diseases.

Objective: The systemic exposure to the drug after topical application.

Design: Open-label, multiple topical dose, non-controlled pharmacokinetic study.

Setting: Referral center, hospitalized and ambulatory care.

Patients: Twelve adult patients with atopic dermatitis. Their extent of affected skin area at baseline ranged from 15% to 59% of the body surface area.

Intervention: Treatment of all lesions with 1% SDZ ASM 981 cream twice daily for 3 weeks. On days 1, 2, 3, 4, 6, 10, and 17 of treatment, and 1 day and 1 week after the last application, blood samples were collected.

Main outcome measure: To determine the SDZ ASM 981 blood concentrations by a radioimmuno-assay.

Results: Of the 444 blood concentrations measured, 78% were below the assay limit of quantitation (LoQ; 0.5 ng/ml). The individual maximum blood concentrations ranged from <LoQ to 1.4 ng/ml except for one contaminated sample (4.6 ng/ml). The area under the concentration-time curve over a 12-h application interval ranged from 0 to 11.4 h•ng/ml. There was no accumulation of SDZ ASM 981 beyond day 2 of treatment. The clinical tolerability was good, both locally and generally.

Conclusion: Three weeks treatment with 1% SDZ ASM 981 cream resulted in consistently low blood concentrations of SDZ ASM 981 with no accumulation over time. SDZ ASM 981 cream appears suitable for the long-term management of atopic dermatitis, with no limitation of extent of skin area to be treated and no limitation of treatment duration.
INTRODUCTION

There is no entirely satisfactory treatment available for atopic dermatitis. The use of systemic therapies is limited by their side effects. Topical medications used for this chronic inflammatory skin disease are coal tar preparations, corticosteroids, antiseptics, antibiotics, and antihistamines. In view of the emphasis on the immunopathogenesis of atopic dermatitis, new inflammatory cytokine inhibitors have been under investigation. Topical application of cyclosporin was not effective, in contrast to topical application of tacrolimus, which proved to be effective in atopic dermatitis.

SDZ ASM 981 is a selective inhibitor of inflammatory cytokines developed specifically for the treatment of inflammatory skin disease. In preclinical studies, SDZ ASM 981 exhibited high anti-inflammatory activity in mouse and pig models of allergic contact dermatitis after topical application. The clinical efficacy and tolerability of twice daily application of 1% SDZ ASM 981 cream has been demonstrated in a randomized, double-blind, placebo-controlled, left-right comparison, proof of concept study in atopic dermatitis patients.

The systemic exposure and the local and systemic safety of repeated topical application of 1% SDZ ASM 981 in man were investigated in an open, non-controlled study in twelve adult patients with moderate to severe atopic dermatitis. Multiple blood levels of SDZ ASM 981 were measured throughout the study.

PATIENTS AND METHODS

Patient population

Adult patients were recruited from the Department of Dermatology of the Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. All patients had atopic dermatitis according to the Hanifin and Rajka criteria, with at least 10% of their total body surface affected. Oral, or inhaled corticosteroids, cyclosporine A or other immunosuppressive agents, phototherapy, and herbal medicines had to be stopped one month before entering the study.

Patients had to be in a good general condition, as reflected by physical examination, hematology, biochemistry, urinalysis, and electrocardiogram. Female patients who were pregnant or breast feeding were excluded.

All patients were informed of the study procedures and gave written informed consent. The study protocol was approved by the local ethics committee.
Chapter 5

Treatment regimen
The patients were treated with 1% SDZ ASM 981 cream twice daily for 21 days. All affected skin areas were treated, including the face and neck. The patients were hospitalized for the first week of treatment and pursued the last two weeks as outpatients. They visited the hospital on day 10, 17, 22, and 29 for performing the study evaluations.

In the first week, the hospital staff applied the study medication twice daily. From the evening of day 6 till the last treatment day, the patients applied the cream twice daily at home, except at the visits of day 10 and day 17 when they applied the medication in the clinic after blood sampling. The patients recorded the times of application on a diary card. The amount of cream applied was determined by weighing the tubes of cream before and after each application during hospitalization, and at each visit during outpatient treatment.

Pharmacokinetic protocol and analytical method

Blood sampling. Venous blood samples were collected on days 1, 2, 3, and 4 over a dosing interval, i.e., just before the morning application of the SDZ ASM 981 cream, and 2, 4, 6, 8, and 12 hours thereafter. On day 6, blood was sampled before and 2, 4, 6, and 8 hours after the morning application. On days 10 and 17, blood samples were taken before and 2, 4, and 6 hours after the application at the clinic. Finally, one sample was taken one day and one week after the last application of the study cream. For each blood sample, 2 ml whole blood was collected into a polystyrene EDTA coated tube. The samples were kept frozen at -20 °C pending analysis. Blood samples were drawn from a catheter put in place before application or on a non treated skin area.

Analytical methods. SDZ ASM 981 blood concentrations were determined by a specific radioimmunoassay method. Sample processing. Briefly, saturated sodium chloride solution (80 μl) was added to each blood sample (200 μl) and after mixing, 2-propanol (2 ml) was added. After mixing, the tubes were centrifuged and the supernatant fraction was decanted and evaporated to dryness at 50°C. Each extract was then reconstituted in an appropriate volume of assay buffer, containing the polyclonal sheep anti-ascomycin antibody and radiolabelled tracer (tritium label). Following incubation at 4°C, charcoal suspension (0.5 mL) was dispensed into each test tube and after centrifugation, the supernatant fraction was decanted into scintillation vials to which scintillation fluid was added (2.5 ml, Optiphase Hisafe-3 from Wallac, Finland cat. no.: CE-9205-21/1200-437). All samples were counted for 10 min. in a beta counter, using an appropriate quenching-curve. Data processing. Data were processed with MULTICALC (Wallac, Finland), using a 4PL interpolation with Log-B/Bo. The study sample concentrations and QC samples were determined from the calibration curve. Intrastudy assay performance was
assessed on the basis of a 9-point calibration curve (0.0, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25.0 and 50 ng/ml SDZ ASM 981) and 4 levels of quality control concentrations (0.5, 3.0, 15 and 45 ng/ml). Interassay precision ranged from 11.2% to 15.7% and the accuracy from -5.9% to 5.4%. The limit of quantitation was 0.5 ng/ml.

Pharmacokinetic parameters.
The maximum blood concentration ($C_{\text{max}}$) and the trough blood concentration 12 h after application ($C_{\text{min}}$) were derived from the individual blood concentration-time profiles. When a profile included at least 3 quantifiable concentrations, the area under the blood concentration-time curve over a dosing interval ($\text{AUC}_{0-12\text{h}}$) was calculated by linear trapezoidal summation from 0 to 12 h. For profiles where no 12-h sample was taken, the concentration at 12 h was assumed to be equal to that measured before application from the same profile. Values below the limit of quantitation were treated as zero.

Efficacy
The SCORAD$^{10}$ was used for the clinical evaluation of the total body. This scoring system is developed by the European Task Force on Atopic Dermatitis, to evaluate treatments in atopic dermatitis. It consists of three constituent parts: the extent, the intensity, and the subjective symptoms. The extent is scored using the 'rule of 9' to determine the percentage of the affected body surface area. For the intensity an average lesion is evaluated for erythema, edema/papulation, oozing/crust, excoriation, and lichenification. The dryness is evaluated at an uninvolved area. These 6 intensity items are all scored on a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe), the sum of these is the value for the intensity (range 0-18). For the subjective symptoms the pruritus and the sleep loss were scored at a visual analog scale (range 0-10). The sum of these two items is the value for the subjective symptoms (range 0-20). The SCORAD is calculated with the formula $A/5+7B/2+C$ ($A=$extent, $B=$intensity, $C=$subjective symptoms). The minimal SCORAD value is 0, the maximum value is 103.

In addition to the total body evaluating system, the Hanifin score$^{11}$ was used for the clinical evaluation of a severely involved target area. This scoring system exists of 6 constituent items: erythema, oozing/crust, papulation, lichenification, excoriation, and pruritus, all scored on a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe). The sum of these 6 items is the value for the Hanifin score (range 0-18). The extent of the area and subjective symptoms are not considered in the Hanifin score.
For consistency, nearly all clinical assessments (>95%) were performed by the same investigator. The subjective symptoms of the SCORAD were scored on a visual analog scale by the patients themselves.

**Tolerability**

Adverse events were recorded throughout the study. Physical examination, vital signs, electrocardiogram, blood chemistry, hematology, and urinalysis were routinely checked.

**RESULTS**

Twelve adults with moderate to severe atopic dermatitis entered and completed the study according to the protocol. These 8 male and 4 female patients were all Caucasians. The mean age was 34.5 years (range 19-45 years). The area affected with atopic dermatitis lesions at baseline ranged from 15 to 59% of the total body surface area. The clinical scores for atopic dermatitis at baseline were 46.1 (range 21-63) for the SCORAD index and 9.4 (range 3-14) for the Hanifin score.

The initial dosings were performed by instructed research nurses. Tubes with 50 gram cream were used. The tubes were weighted before and after the application. The initial mean amount of cream applied on day 1 (morning, evening) was 3.9 g for the patient with 15% of the body surface area involved and 16.4 g for the patient with 59% of the body surface area involved. In the whole 3-week treatment period, the amount of cream used ranged between 0.5 to 34 g per application.

**Pharmacokinetics**

A total of 445 blood samples for determination of SDZ ASM 981 were collected from the 12 patients. Because one sample contained an insufficient amount of blood, 444 samples were analyzed. Of these, 78% had concentrations below the limit of quantitation (LoQ: 0.5 ng/ml). Figure 1 is a synoptic view of all quantifiable concentrations (100 values) in the 12 patients. Figure 2 shows the concentration time profile for the patient who had the largest area treated (59% of his body surface area at baseline) and the highest systemic exposure over the study period. Over all patients, the quantifiable concentrations ranged from 0.5 to 1.4 ng/ml except for one outlying value at 4.6 ng/ml (Figure 1). This isolated value was measured on day 3, 2h after application from a blood sample documented to have been taken on a skin area treated with 1% SDZ ASM 981 cream. It was considered to result from a contamination of the blood
**Figure 1** Synoptic plot of the quantifiable blood concentrations of SDZ ASM 981 measured in 12 patients during three weeks of twice daily treatment with 1% SDZ ASM 981 cream (The high blood level value at 4.6 ng/ml is a documented contamination). (LoQ = Limit of Quantitation = 0.5 ng/ml).

**Figure 2** The concentration time profile of patient 2 who had the largest area treated (lesions on 59% of his body surface area at the start of the treatment), and the highest systemic exposure to SDZ ASM 981 over the study period (LoQ = Limit of Quantitation = 0.5 ng/ml, values below the LoQ set to zero)
sample and excluded from parameter calculation. The quantifiable concentrations displayed no proper peak over a dosing interval nor over the entire treatment period, as illustrated in Figures 1 and 2. Beyond day 2 of treatment, the concentrations did not further increase, indicating no accumulation over longer times of treatment. One day and one week after the last cream application nearly all concentrations were below the limit of quantitation. The individual $C_{\text{max}}$ ranged from 0 (not quantifiable) to 1.4 ng/ml. The individual $C_{\text{min}}$ ranged from 0 to 0.8 ng/ml. The individual $\text{AUC}_{0-12\text{h}}$ ranged from 0 to 11.4 ng h/ml. Since most values were 0, i.e. <LoQ, no statistics were calculated on $C_{\text{max}}$, $C_{\text{min}}$, and $\text{AUC}_{0-12\text{h}}$.

There was no significant relationship between the extent of lesional body surface area at baseline (day 1 of treatment) and the individual maximum $\text{AUC}_{0-12\text{h}}$ over the treatment period (Figure 3, $p=0.08$).

![Figure 3](image)

**Figure 3**

*Maximum $\text{AUC}_{0-12\text{h}}$ versus the involved body surface area (BSA) at day 1*
Efficacy
The mean (± 2 SEM) percent change from baseline for the Hanifin score and the SCORAD index over the whole study period is shown in Figures 4 and 5, respectively. Table 1 provides the mean and standard deviation for the Hanifin score, the SCORAD index, and its three components (extent and intensity of disease and subjective symptoms). In general, all scores showed a rapid decrease during the first 6 days of treatment (up to -56.9% for the Hanifin score). Beyond the first week, the scores remained stable with minor fluctuations, except for the extent of disease score which continued to decrease until day 17. One week after treatment discontinuation (day 29) the improvement was still greater than 50% for the Hanifin score, the SCORAD extent, and the SCORAD pruritus and sleep loss.

<table>
<thead>
<tr>
<th></th>
<th>Day 6</th>
<th>Day 10</th>
<th>Day 17</th>
<th>Day 22</th>
<th>Day 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanifin score</td>
<td>-56.9 (16.5)</td>
<td>-55.9 (21.2)</td>
<td>-53.0 (30.3)</td>
<td>-59.5 (24.4)</td>
<td>-52.3 (27.0)</td>
</tr>
<tr>
<td>SCORAD index</td>
<td>-46.3 (12.6)</td>
<td>-45.8 (6.9)</td>
<td>-52.6 (17.9)</td>
<td>-48.6 (15.0)</td>
<td>-41.2 (23.5)</td>
</tr>
<tr>
<td>SCORAD extent</td>
<td>-48.2 (19.8)</td>
<td>-58.6 (15.2)</td>
<td>-66.0 (8.1)</td>
<td>-60.9 (20.3)</td>
<td>-59.1 (30.1)</td>
</tr>
<tr>
<td>SCORAD intensity</td>
<td>-42.4 (17.2)</td>
<td>-41.3 (13.1)</td>
<td>-47.2 (18.3)</td>
<td>-42.0 (18.2)</td>
<td>-31.9 (17.9)</td>
</tr>
<tr>
<td>SCORAD pruritus</td>
<td>-45.1 (51.8)</td>
<td>-48.8 (30.8)</td>
<td>-60.0 (40.3)</td>
<td>-59.4 (15.9)</td>
<td>-56.7 (39.4)</td>
</tr>
</tbody>
</table>

Table 1 Mean percent change (%) from baseline and (standard deviation) for the Hanifin score, the SCORAD index and its three components, extent (A), intensity (B), and subjective symptoms of sleep loss and pruritis (C) at Days 6, 10, 17, 22, and 29 (end of study).
Figure 4:
Hanifin score: percent change from baseline. Plot of mean response, vertical bars show twice standard error of mean (EOS = End of Study = day 29).

Figure 5
SCORAD index: percent change from baseline. Plot of mean response, vertical bars show twice standard error of mean (EOS = End of Study = day 29).
SDZ ASM 981: Short-term pharmacokinetics

Tolerability
All patients enrolled in the study were in general good health. There were no clinically relevant changes in physical examination, vital signs, electrocardiograms, hematology, or biochemistry parameters during the course of the study.

The tolerability of the 1% SDZ ASM 981 cream was assessed by the investigator and the patients as good. No serious adverse event occurred during the study. The most frequent adverse event reported was a mild and transient feeling of warmth/burning at the site of application of the cream, experienced by 6 patients. This event started after the first application in 5 of the 6 patients and did not lead to discontinuation of treatment in any of them. Phlebitis at the site of insertion of the catheter occurred in 3 patients but did not extend. Mild folliculitis was observed in two patients.

DISCUSSION
This study was specifically designed to determine the SDZ ASM 981 blood concentrations during twice daily treatment for three weeks with the 1% cream in twelve adult patients with moderate to severe atopic dermatitis. Intensive pharmacokinetic sampling was performed. The SDZ ASM 981 blood concentrations were consistently low in all patients, most values being non quantifiable. For the patients who had quantifiable values, SDZ ASM 981 concentrations fluctuated in general between the LoQ and twice the LoQ. They displayed a low plateau with no peak exposure neither over an application interval nor over the entire treatment period. The single high value of 4.6 ng/ml measured in a patient on his third day of treatment, 2 hours after the morning application of the 1% SDZ ASM 981 cream was considered to result from a contamination of the blood sample by SDZ ASM 981 cream. Indeed, this sample was documented to have been taken by venipuncture on a skin area (elbow fold) treated with the 1% SDZ ASM 981 cream, due to technical problems with the catheter. Subsequent blood samples were collected 4, 6, 8, and 12 hours after cream application, with a new catheter on a non treated site. Blood levels measured in this patient on day 3 before and 4, 6, 8, and 12 hours after cream application were 0.7, 0.8, 0.7, 0.6, 0.8 ng/ml, respectively. All other blood samples (N=33) collected during the study in this patients on day 1, 2, 4, 6, 10, and 17 resulted in SDZ ASM 981 concentrations from <LoQ to 0.8 ng/ml.

There was no evidence for accumulation after repeated applications nor for continued release of the drug from the skin after treatment discontinuation. SDZ ASM 981 blood levels during longer term treatment will be studied in further
clinical trials. In light of the low concentration range observed, the relationship between the extent of lesions and the systemic exposure was difficult to explore. However, even the patients with the largest extent of skin area involved displayed consistently low SDZ ASM 981 blood concentrations.

In all patients, and excluding the value associated with a contaminated sample, the blood concentrations ranged from <LoQ to 1.4 ng/ml. For comparison, in a 13-day subcutaneous (sc) toxicology study in rats, the animals showed neither adverse effects nor signs for systemic immunosuppression at the highest dose tested, that was 9 mg/kg sc. Mean ± SD plasma levels measured 24 h after the last administration was 193 ± 120 ng/ml\(^1\)

The interpretation of tolerability data is limited by the small number of patients and the open non-controlled design of the study. The feeling of warmth/burning was the most frequently reported adverse event. It was transient, always rated as mild, and did not lead to treatment discontinuation in any patient. The phlebitis in three patients was caused by the catheter used for blood sample collection. Atopic patients are known to have their skin largely colonised by bacteria and therefore to be prone to this type of complication when a catheter is left in place for several days. In subsequent patients, the catheters were replaced more often and this side effect was not observed anymore.

The interpretation of efficacy is also limited by the non-controlled study design. In these twelve patients with moderate to severe disease, SDZ ASM 981 1% cream appeared to induce a marked reduction of signs and symptoms as evaluated by the SCORAD and Hanifin scores. The improvement may have been facilitated during the first week of treatment by the fact that the patients were hospitalized and therefore withdrawn from environmental co-factors. One week after the end of treatment the improvement of the dermatitis was still significant. This suggests that SDZ ASM 981 does not provoke a rebound effect (excessive worsening) after discontinuation of treatment, as typically seen with treatments such as oral corticosteroids.

A clear relation between SCORAD index and amount of cream used could not be expected. The SCORAD consist on three parts: area, intensity and subjective signs. The area represents approximately 20% of the SCORAD index. The dose only depends on the area, regardless of the intensity or subjective symptoms.

In conclusion, three weeks twice daily treatment of atopic dermatitis patients with extensive lesions (up to 59% of body surface area) with the 1% SDZ ASM 981 cream resulted in low SDZ ASM 981 blood concentrations and in no accumulation over time. These results indicate that SDZ ASM 981 cream may be safe for long-term use with no limitation in the extent of skin area treated and no restriction for the treatment of sensitive skin areas such as the face.
Acknowledgment

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REFERENCES


