Development of new treatment modalities for atopic dermatitis
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Chapter 6

Long-term pharmacokinetics of pimecrolimus (SDZ ASM 981, Elidel®) in atopic dermatitis

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Submitted for publication
Chapter 6

SUMMARY

Objectives: Primary objective: To determine blood concentrations of pimecrolimus when applied as the 1% final market formulation (FMF) cream twice daily intermittently for up to 12 months to the lesional skin in patients with moderate to severe atopic dermatitis. Secondary objective: To investigate the long-term safety of the 1% pimecrolimus cream when applied intermittently for up to 12 months in patients with moderate to severe atopic dermatitis. And to investigate the efficacy of the 1% pimecrolimus FMF cream in patients with moderate to severe atopic dermatitis treated intermittently for up to 12 months.

Design: This open-label, multiple topical dose study consisted of a 13-day (day -14 to -2) screening period, a treatment period of up to 12 months and a post-treatment day (day 1 of month 13 or the day after the last application of Pimecrolimus). The forty (40) male or female adult patients (min 18 years of age) with moderate to severe atopic dermatitis and a total body surface area (TBSA) involvement of ≥20% attended visits to the clinic at screening, day 1, week 1, 3 and 6 of treatment, then monthly during the treatment period and at study completion (post-treatment day). The patients were treated as outpatients with the 1% pimecrolimus cream which had to be applied twice daily on all their dermatitis lesions, including those on the face, for up to 12 months.

Criteria for evaluation: Safety: Physical examination, vital signs, and laboratory evaluations. Efficacy: Overall evaluation score of dermatitis and the Eczema Area and Severity Index (EASI) were to be performed at the week 1, 3 and 6 visit, at each monthly visit, and at study completion. Pharmacokinetics: Blood samples for determination of pimecrolimus concentrations were to be collected at screening (blank sample), and at each site visit (before, 2 and 4 hours after the morning application). If the patient was not under treatment at the time of the visit, only one sample was to be collected at any time during this visit. pimecrolimus concentrations were determined in whole blood using a Radio Immuno Assay (RIA) with a limit of quantitation (LoQ) of 0.5 ng/ml.

Results: Forty (40) patients, 21 males and 19 females, aged from 19 to 59 years, with moderate to severe atopic dermatitis entered the study. Twenty (20) of them completed 6 months and 13 completed 1 year in the study. The individual blood concentrations of pimecrolimus measured between day 1 and month 12 of treatment in the 40 patients enrolled in the study were consistently low. Of the 918 concentrations determined (excluding the blank samples taken at screening), 98% (900 concentrations) were below the limit of quantitation of 0.5 ng/ml. The maximum concentration observed throughout the entire study was 0.8 ng/ml. Efficacy: According to the investigator's overall evaluation of dermatitis, 60% of patients had their eczema cleared by at least 50% at their
Long term pharmacokinetics of pimecrolimus

end-of-study evaluation compared to baseline, 35% had their eczema cleared by less than 50%, and one patient had worsened during the study.

**Conclusions:** In patients with extensive atopic dermatitis lesions (up to 61.5% of body surface area affected at baseline) treated twice daily with 1% pimecrolimus cream for up to 12 months, blood concentrations of pimecrolimus were consistently low. There was no systemic accumulation over the treatment period of up to 12 months. There was no evidence for increases in blood concentrations in patients with larger areas of body surface under treatment. pimecrolimus FMF 1% cream applied twice daily for up to 12 months showed a good local and systemic tolerability. The efficacy data in this study were comparable to the current experience with the 1% pimecrolimus cream in the indication atopic dermatitis.

**INTRODUCTION**

Pimecrolimus (SDZ ASM 981, Elidel®) is a novel ascomycin derivative being developed for the topical treatment of atopic dermatitis. The clinical efficacy of pimecrolimus has been confirmed in adults by proof-of-concept studies in atopic dermatitis for a 1% cream(1). The present study, conducted in parallel to a long-term safety and efficacy study, was designed to determine blood concentrations of pimecrolimus, and to evaluate the safety of the 1% cream in patients with moderate to severe atopic dermatitis during long-term (up to 12 months) management of their disease. Efficacy of the 1% cream was explored as a secondary objective.

The 1% pimecrolimus cream had already been demonstrated to be effective in adult atopic dermatitis(2). After 3-week treatment of extensive lesions in moderate to severe atopic patients(3), the pimecrolimus blood concentrations remained low, with no accumulation, and well below levels at which systemic effects, in particular signs of immunosuppression, were observed in the toxicology studies. The main objective of the present study was to provide information on the potential systemic accumulation of pimecrolimus after long-term treatment with the 1% cream.

**Study objectives**

*Primary objectives* To determine blood concentrations of pimecrolimus when applied as the 1% cream twice daily intermittently for up to 12 months to the lesional skin in patients with moderate to severe atopic dermatitis. *Secondary objectives* To investigate the long-term safety of the 1% pimecrolimus cream when applied intermittently for up to 12 months in patients with moderate to severe atopic dermatitis and to investigate the efficacy of the 1% pimecrolimus...
cream in patients with moderate to severe atopic dermatitis treated intermittently for up to 12 months

**Overall study design**

This open-label, multiple topical dose study consisted of a 13-day (day -14 to -2) screening period, a treatment period of up to 12 months and a post-treatment day (day 1 of month 13 or the day after the last application of pimecrolimus cream). The patients attended the clinic at screening, day 1, week 1, 3 and 6 of treatment, then monthly during the treatment period and at study completion (post-treatment day). Each visit was allowed to be attended within a window of ±3 days around the scheduled visit.

The patients, who had given their written informed consent before entering the study, were treated as outpatients with the 1% pimecrolimus cream which had to be applied twice daily on all their dermatitis lesions, including those on the face, for up to 12 months. During the study, when patients observed complete clearance of their inflammation and did not experience any pruritus, they were asked to stop pimecrolimus treatment and to restart as soon as their dermatitis recurred. Patients were allowed to stop therapy on the cured lesions while continuing to apply study medication on the more severe or persistent inflammatory lesions. The patients were encouraged to use emollients liberally on all affected (one hour after pimecrolimus application) and non-affected skin areas, and in skin disease-free intervals on the entire skin (i.e. when inflammation and pruritus completely ceased and no study medication was applied).

The first application on day 1 was performed in the clinic under the supervision of the investigator or authorized staff. If subsequent visits took place during a treatment period, the patients were instructed to attend the clinic in the morning before pimecrolimus application. The study medication was to be applied at the clinic since pharmacokinetic blood samples were to be taken. The tube(s) of cream used were weighed before and after these applications in the clinic. At each visit, all tubes dispensed were to be returned to the clinic and weighed. Applications at home, adverse events and concomitant medications (including emollients) were to be recorded on patient diary cards.

Blood samples were collected at the site visits to determine pimecrolimus blood concentrations and to perform safety laboratory tests. Pimecrolimus blood concentrations were monitored during the study.
Study population
Originally, 20 male or female adult patients, aged 18 and above, with moderate to severe atopic dermatitis were planned to be included to get safety and blood concentration data of at least 15 patients treated for at least 6 months with pimecrolimus. Due to the high discontinuation rate during the first months of study treatment, the number of patients was increased to 40 patients. The patients had to have a total body surface area (TBSA) involvement of $\geq 20\%$ as determined by the rule of nine, and had to fulfill the diagnostic criteria of Hanifin and Rajka for atopic dermatitis(4). Female patients had to be post-menopausal, surgically sterilized or under reliable contraception for at least 3 months before inclusion into the study. Patients who met the above criteria and were already enrolled in the 3-week pharmacokinetic study(3) or had completed a 3-week dose finding(2) study were considered as eligible. Before entering study, all patients had to give their written informed consent.

Patients excluded were those with any concurrent disease or treatments that could interfere with the study evaluations:

- treated with photo therapy or systemic therapy (steroids, cyclosporin A, herbal medicines, etc) for their atopic dermatitis within 1 month prior to the first study drug application
- treated with topical therapy (tar, topical corticosteroids, etc) not stopped 24 hours prior to first study drug application
- treated with radiation therapy, systemic therapy with cytostatics or immunosuppressive drugs other than those mentioned above within 24 weeks prior to first application of trial medication
- treated with investigational drugs, with the exception of previous treatment with pimecrolimus (which was allowed), within 8 weeks prior to first application of study medication
- diagnosed with: serious adverse reactions or hypersensitivity to macrolides or any ingredients of the study medication;
- with acute or chronic bacterial, viral or fungal diseases (patients with active herpes labialis and/or genitalis were to be excluded; patients with verrucae vulgaris, tinea pedis and/or onchomycosis could be included if the treated areas were not affected);
- with a history or clinical evidence of cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematologic, neurologic disease, unstable metabolic or endocrine disorders,
- disease other than atopic dermatitis;
- with a history or presence of malignancy including skin cancer, or lymphoproliferative disorders;
- with a history of serious mental disorders.
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Treatments

Investigational drug: 50 g tubes of 1% pimecrolimus cream, final market form (FMF). The patients were instructed to use the tubes sequentially (i.e., to finish tube 1 before starting tube 2). At each site visit, the patients had to bring back all medication tubes. At the end of the study, all used, partially used and unused tubes were to be collected by the investigator.

Concomitant therapy No systemic or topical treatment for atopic dermatitis, except the use of emollients and/or antihistamines (if considered necessary by the investigator), was allowed during the study. Patients were encouraged to use emollients on affected (one hour after application of active treatment), non-affected skin areas and in disease free intervals on the entire skin (i.e., when inflammation and pruritus had completely ceased). If systemic/topical therapy for atopic dermatitis (with the exception of antihistamines) was given [more than 2 administrations of oral corticosteroids or more than 2 weeks with topical steroids (excluding medications under study)], this was treated as a major protocol violation. Oral antibiotics could be used to treat bacterial infections of the skin (if considered necessary by the investigator), while topical antibiotics were to be avoided. Topical antifungals could be used if antifungal treatment was indicated.

Treatment compliance Patients were interviewed at the scheduled visits during the treatment phase with regard to compliance. They had to present the completed diary cards to the investigator at each visit to demonstrate that study medication was applied according to the protocol. Diary cards (carbon pages) were to be posted by the patient to the study center every 2 weeks. This was to encourage the patients to fill in the diary cards regularly.

Study conditions and restrictions
The following measures were taken to minimize the risk of contamination of the pharmacokinetic blood samples by the pimecrolimus cream:

- After each study drug application, hands were to be washed.
- The person performing the blood withdrawal procedure was not allowed to be involved in pimecrolimus cream application and to manipulate the opened pimecrolimus tubes.
- At the site visits occurring during a treatment period, a cannula for blood sampling was applied before cream application.
- The skin site where blood samples were drawn had not to come into contact with the study medication; e.g., a site for blood sampling was selected beforehand and protected by a plaster.
- Care was also to be taken not to contaminate any blood sampling material with the cream. Sampling was performed in a room where no application had been performed and no cream had been disposed or stored.
**Long term pharmacokinetics of pimecrolimus**

**Safety assessments**
Safety assessments consisted of monitoring and recording all adverse events (including but not limited to local tolerability of study medication and bacterial, viral or fungal infections) and serious adverse events, the regular monitoring of hematology, biochemistry and urine values, regular measurement of vital signs and the performance of physical examination.

**Pharmacokinetic assessments**
At each sampling time 2 ml (4 ml at screening, only) venous blood was taken at a site where no pimecrolimus cream was applied. The blood was drawn into EDTA coated polypropylene tubes at the following time points:
- at screening: one blank sample
- at 0, 2 and 4 hours after pimecrolimus cream application if the patient was under treatment at the time of the visit or one blood sample at any time during the out-patient visit in that month if the patient was not under treatment at the time of the visit

All samples were kept frozen at <-20°C pending analysis. pimecrolimus blood concentrations were determined using a Radio Immuno Assay (LoQ = 0.5 ng/ml).

**Efficacy assessments**
*Overall evaluation score* An overall evaluation of the atopic dermatitis was to be performed by the investigator and patient: see table 3.

*Eczema area severity index (EASI)* The EASI(5) assigned proportionate body surface areas to the head and neck [10%], trunk [30%], upper extremities [20%] and lower extremities [40%]. This was roughly consistent with the rule of nine. The area of involvement of each of the four body regions was represented by a numeric coded value [0 - 6] as shown in Table 4.

The head, trunk, upper limbs and lower limbs were assessed separately for erythema (E), infiltration/papulation (I), excoriation (EX) and lichenification (L). The average degree of severity of each symptom in each of the four body parts was assigned a score of 0-3 indicating none (0), mild (1), moderate (2) and severe (3) expression of the clinical sign. The area affected by inflammation (not including dry skin) on each body part was estimated as a percentage of the total area of that particular body part and a score from 0-6 was then assigned. The EASI was then calculated by a formula.
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<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>100% (completely) clear of signs and symptoms of dermatitis</td>
</tr>
<tr>
<td>1</td>
<td>90%-99% (almost) clear with few signs and symptoms of dermatitis remaining at treated areas</td>
</tr>
<tr>
<td>2</td>
<td>75%-89% (markedly) clear with some signs and symptoms of dermatitis remaining at treated areas</td>
</tr>
<tr>
<td>3</td>
<td>50%-74% (moderately) clear with notable signs and symptoms of dermatitis remaining at treated areas</td>
</tr>
<tr>
<td>4</td>
<td>25%-49% (minimally) clear with signs and symptoms of dermatitis remaining at treated areas</td>
</tr>
<tr>
<td>5</td>
<td>0%-24% (unclear) with very marked signs and symptoms of dermatitis remaining at treated areas</td>
</tr>
<tr>
<td>6</td>
<td>Extreme involvement with gross signs and symptoms of dermatitis</td>
</tr>
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</table>

Table 3: Overall evaluation score

<table>
<thead>
<tr>
<th>Area Involvement</th>
<th>body surface area</th>
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<tbody>
<tr>
<td>0</td>
<td>no eruption</td>
</tr>
<tr>
<td>1</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>2</td>
<td>10% - 29%</td>
</tr>
<tr>
<td>3</td>
<td>30% - 49%</td>
</tr>
<tr>
<td>4</td>
<td>50% - 69%</td>
</tr>
<tr>
<td>5</td>
<td>70% - 89%</td>
</tr>
<tr>
<td>6</td>
<td>90% - 100%</td>
</tr>
</tbody>
</table>

Table 4: EASI: area of involvement

96
Pruritus was assessed separately using a score ranging from 0-3, representing none (0), mild (1), moderate (2) and severe (3) pruritus. Pruritus was assessed by the intensity of itch during the previous 24 hours.

Statistical methods

**Sample size determination:** Appropriate sample size and power could not be determined due to the preliminary nature of the study. The sample size has, therefore, been chosen based on practical considerations. **Safety and tolerability evaluations** All patients who received at least one treatment were included in the safety and tolerability evaluation. **Pharmacokinetic evaluations** All patients who received at least one treatment were included in the pharmacokinetic data analysis. Biofluid concentrations were expressed in mass per volume units. All concentrations below the limit of quantitation or missing data were labeled as such in the concentration data listings. Concentrations below the limit of quantitation were treated as zero. **Pharmacokinetic variables** As the vast majority of blood samples collected contained concentrations of pimecrolimus below the limit if quantitation, determination of standard pharmacokinetic parameters was not possible. Individual blood concentrations of pimecrolimus were tabulated and plotted versus time and body surface area affected to explore any relationships between exposure and these parameters. **Efficacy variables** The efficacy variables were evaluated for the following two populations: Intent to treat (ITT) population with the last observation carried forward (LOCF) and Patients under treatment (PUT) with observed cases, excluding the 3 protocol violators. **Overall evaluation of dermatitis** An overall evaluation of the patient's dermatitis, on a 7-point ordinal scale, was performed by the investigator and the patient. Individual scores of the overall evaluation of dermatitis were listed by patient and visit. For both populations (ITT and PUT), the frequency of the overall evaluations scores was shown for week 1, month 6 and month 12. Eczema Area Severity Index (EASI) Individual data of the EASI were listed by patient and visit. For both populations (ITT and PUT), descriptive statistics of the EASI were presented for month day 1 (baseline), month 6 and month 12. In addition, the percentage change from baseline was displayed for month 6 and month 12.
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RESULTS

Subject disposition
Forty (40) patients (21 males, 19 females) with moderate to severe atopic dermatitis entered the study, 37 were Caucasian and 3 were Oriental. Individual demographic data and descriptive statistics are shown in the table 1.

These patients presented atopic lesions on 13.5% to 61.5% of their body surface area at baseline (day 1) as calculated from the EASI. Twenty (20) of them completed 6 months and 13 completed 1 year in the study. Of the 27 patients who did not complete the study, 22 patients discontinued due to an unsatisfactory therapeutic effect, 2 patients due to adverse events and 3 patients were lost to follow-up. At screening, the patients presented moderate to severe atopic dermatitis with an extent of disease (as determined by the rule of nine) ranging from 20 to 61.5% of their total body surface area. A total of 5 patients participated in a previous 3-week pharmacokinetic study and 14 patients participated in the 3-week dose-finding study.

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>(minimum - maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>33.9</td>
<td>(19 - 59)</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>176.9</td>
<td>(159 - 203)</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>75.0</td>
<td>(56 - 150)</td>
</tr>
</tbody>
</table>

Table 1: Demographic characteristics at screening [n=40]

Medications at screening and baseline
A total of 31 patients used topical corticosteroids before the first application of pimecrolimus; One patient took an oral corticosteroid until one month before the first application of the study medication. Eight (8) patients used inhaled corticosteroids for the treatment of asthma or hayfever before the start of the study. Five patients stopped the treatment before the first study drug application, whereas three patients continued throughout the study. Nineteen patients received antihistamines for the treatment of atopic dermatitis or hayfever already before the study start, and continued during study treatment. Thirteen female patients took oral contraceptives throughout the entire study. Twenty-eight (28) patients applied emollients not containing active ingredients throughout the entire study.
Dosage administration and drug dispensing
The individual amount of cream applied during the site visits ranged from 0.1 to 16.8 g, and the mean value decreased from 5.3 g (± 4.0 SD) at the day 1 visit to 2.3 g (± 2.7 SD) at the month 12 visit. The individual amount of cream applied per day at home ranged from 0.1 to 28.1 g, and the mean amount was 9.2 g (± 7.1 SD) in the first week of the study (between day 1 and week 1 visit), and 3.5 g (± 3.0 SD) at the end of the study treatment (between month 11 and month 12 visit). Based on the weights of cream recorded during the entire study period, the compliance was judged good.

Safety and tolerability results
Serious adverse events One serious adverse event occurred during the study. Patient was hospitalized for 2 weeks due to multiple bone fractures sustained in a traffic accident in month 5 of study treatment. The study medication was interrupted for few days, but otherwise the patient completed the study according to the protocol. The investigator did not suspect a relationship between this event and the study medication. Adverse events In summary, twice daily applications of 1% pimecrolimus cream up to 1 year were well tolerated, both locally and systemically. Thirty-six (36) of the 40 patients, who entered the study, reported a total of 173 adverse events (including the above mentioned serious adverse event). Of the 36 patients, 21 had at least one mild adverse event, 23 at least one moderate and 19 at least one severe. Twenty-five (25) patients had adverse events suspected to be study drug related, and 26 patients had adverse events not suspected as related to the study medication. The most frequently observed adverse events with a suspected study drug relationship, which were reported by more than 1 patient, are summarized in the table 2.

The other adverse events which the investigator considered as study drug related occurred in single patients only. They consisted of mild herpes simplex, severe burning on all skin, severe eye irritation, moderate/severe nervousness, moderate pigmentation disorders, mild impetigo, mild yellow skin, mild peripheral swelling and severe face oedema. Other frequently observed adverse events were headache, influenza and nasopharyngitis; but, the investigator considered none of them as study drug related.

Two patients discontinued the study in month 3 of treatment due to adverse events; one patient due to severe pruritus, application site burning, and nervousness, and one patient due to worsening of pigmentation disorders. The investigator considered these 4 adverse events as drug related.
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<table>
<thead>
<tr>
<th>Adverse events (preferred term)</th>
<th>Total number of Patients*</th>
<th>Number of patients by severity**</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site burning</td>
<td>12</td>
<td></td>
<td>4</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Application site reaction</td>
<td>6</td>
<td></td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td></td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2</td>
<td></td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

* number of patients with at least once the adverse event, regardless of severity
** number of patients with at least once the adverse event of the given severity

Table 2: Number of patients with the most frequently observed adverse events (reported by > 1 patient), suspected as drug related, grouped by severity; n=40

Concomitant medications
Three patients who received more than 2 administrations of an oral corticosteroids during treatment with study medication are described as protocol violators. In the following paragraphs, those patients are summarized who used corticosteroids during the study, but within the limits allowed by the protocol. One patient (no. 3) received two oral doses of a corticosteroid for the treatment of worsening of his atopic dermatitis which was not controlled by the study medication.

Fourteen (14) patients applied topical corticosteroids over 1 to 10 days during study treatment due to worsening of atopic dermatitis. Six patients used topical corticosteroids within 1 to 5 days after the last application of pimecrolimus for the treatment of their atopic dermatitis. Seven patients received inhaled corticosteroids during application of study medication for the treatment of hayfever or asthma, which was allowed by the protocol. Twenty-nine (29) patients received oral antihistamines during the study period for the treatment of atopic dermatitis or hayfever.

Clinical laboratory findings
Laboratory evaluations (biochemistry, hematological, urinalysis) were performed at screening, during treatment (week 3, and month 7) and at study completion. In summary, all subjects showed slight deviations from the normal
range for at least one biochemistry and/or hematology parameter. However, the investigator considered none of these abnormalities as clinically relevant or drug related. Twenty-eight (28) patients showed eosinophil counts above the upper limit of normal at different time points during the study with the maximum value of 25.1% (normal range 0-5.3%) Twenty-two (22) patients exhibited elevated eosinophil counts already at screening. Eosinophil elevations were expected in this atopic population. The investigator considered none of these deviations as clinically relevant. Twenty-four (24) patients had monocyte counts above the upper limit of normal at different time points during the study with the maximum value of 14.4% (normal range 2-9%) occurring in patient 12 at screening. Twelve (12) patients exhibited elevated monocyte counts already at screening, which did not show an increasing trend during the study. The investigator considered none of these deviations as clinically relevant.

Urinalysis Twenty-one (21) patients had abnormal values for at least one of the urinalysis parameters at different time points during the study; 11 patients for hemoglobin, 7 for leucocytes, 6 for protein, and 1 for glucose. These findings were considered to be neither drug related nor clinically relevant. Pregnancy test For all 19 female patients, the urine pregnancy tests were negative. Vital signs None of the patients showed a clinically relevant change of the body weight during the study compared to screening. All patients had a normal body temperature below 37.5 °C. None of the patients showed any clinically relevant abnormalities neither for the blood pressure nor the pulse rate.

**Pharmacokinetic results**

The individual blood concentrations of pimecrolimus measured between day 1 and month 12 of treatment in the 40 patients enrolled in the study. The blood concentrations measured during study treatment were consistently low. Of the 918 concentrations determined (excluding the blank samples taken at screening) 98% (900 concentrations) were below the limit of quantitation of 0.5 ng/ml (Figure 7.4-1). The maximum concentration observed throughout the entire study was 0.8 ng/ml.

There was no evidence for systemic accumulation of pimecrolimus during multiple topical administration up to 1 year. Blood concentrations remained low even in the patients with the largest body surface area treated (up to 61.5% BSA affected on day 1).

**Efficacy results**

The efficacy of study treatment was evaluated by means of the Eczema Area Severity Index (EASI) and an overall evaluation of dermatitis performed by the investigator and the patient. As mentioned above, the efficacy variables were evaluated for the following two populations: Intent to treat (ITT) population
with the last observation carried forward (LOCF) and patients under treatment (PUT) with observed cases, excluding the 3 protocol violators.

**Overall evaluation of dermatitis** For patient 24, no data were available for the overall evaluation of dermatitis at the week 1 visit. Thus, this patient could not be included in the ITT and PUT population.

**Overall evaluation by the investigator** For the ITT (with LOCF) population, according to the investigator's judgement at the last individual visit (reported as month 12), 60% of patients had their eczema cleared by at least 50% at their end-of-study evaluation compared to baseline, 35% had their eczema cleared by less than 50%, and one patient had worsened during the study. For the PUT population, at the week 1 visit 23 of the 35 patients had their eczema cleared by at least 50%, at the month 6 visit 12 of the 16 patients, and at the month 12 visit 9 of the 12 patients.

**Overall evaluation by the patient** For the ITT (with LOCF) population, according to the patient's judgement at the last individual visit (reported as month 12), 52.5% of patients had their eczema cleared by at least 50% at their end-of-study evaluation compared to baseline, 42.5% had their eczema cleared by less than 50%, and one patient had worsened during the study. For the PUT population, at the week 1 visit 20 of the 35 patients had their eczema cleared by at least 50%, at the month 6 visit 10 of the 16 patients, and at the month 12 visit 10 of the 12 patients.

**Eczema area severity index (EASI)** The range was 13.5% to 57.0% (median 33.0) at baseline (day 1), 2.0% to 70.0% (median 9.0) at month 6, and 2.0% to 25.0% (median 8.0) at month 12.

At baseline, mean EASI scores were similar for both the ITT (with LOCF) and PUT population. After 6 months treatment, the mean EASI score decreased similarly for both populations. After 12 months treatment, the mean EASI score remained stable for the ITT population (with LOCF), whereas it further decreased for the PUT population, indicating that patients with less improvement discontinued the study.

The mean EASI change from baseline was similar after 6 and 12 months of treatment for both populations; however, the level of disease improvement was consistently better for the PUT population. Thus, it appears that the discontinuations due to an unsatisfactory therapeutic effect occurred mainly during the first 6 months of study treatment.

The individual EASI values and the mean (except 3 protocol violators) are shown in Figure 3.
Long term pharmacokinetics of pimecrolimus

FIGURES

**Figure 1A:**
Pimecrolimus blood concentrations at various times during 12 months treatment (The numbers refer to the number of values superimposed on each symbol)

**Figure 1B:**
Body surface area affected on day 1 versus pimecrolimus blood concentrations

In the patients who were not under treatment at the site visits, the blood concentrations were all below the assay limit of quantitation.
Figure 2:
Median and ranges of the affected body surface area determined from the EASI evaluation at each site visit
Figure 3:
Eczema area severity index (EASI) over time with mean value (solid line) and individual values (shaded lines); n=37, 3 patients were excluded (protocol violators)
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DISCUSSION

Pharmacokinetics
Pimecrolimus blood concentrations measured in 40 patients with moderate to severe atopic dermatitis treated twice daily with the 1% cream onto their lesional skin affecting up to 61.5% of their body surface area for up to 1 year were consistently low. The majority of the concentrations (98%) were below the assay LoQ (0.5 ng/ml). The quantifiable blood concentration range (0.5-0.8 ng/ml) was similar to or less than the range measured in adults treated under the same dosing regimen for 3 weeks(3). It was considerably lower than the maximum blood levels observed at steady-state after well tolerated oral administration of 60 mg/day pimecrolimus for 4 weeks in adult psoriatic patients (mean Cmax 54.5 ng/ml) [data on file, Novartis Pharma]. There was no evidence for increase in blood concentrations of pimecrolimus over the 1 year treatment period thus indicating the absence of systemic accumulation of pimecrolimus during long-term management of atopic dermatitis. Similarly, there was no evidence for increasing blood concentrations in patients with larger body surface area affected and treated (up to 61.5% BSA). This result was consistent with the 3-weeks pharmacokinetic study(3). Given the low blood concentrations measured in these patients, the high proportion of levels below the LoQ, and the impossibility to calculate AUCs, no formal pharmacokinetic/pharmacodynamic (safety-efficacy) analysis was performed in this study.

Most of the patients took corticosteroids and antihistamines prior to and some of them also during the study. However, no interference of these drugs with the bioanalytical assay of pimecrolimus in blood was evidenced since all the blank blood samples collected at screening, prior to first pimecrolimus application, showed no increased background signal and no non-specific binding in the assay.

Safety and tolerability
Twice daily applications of 1% pimecrolimus cream up to 1 year were well tolerated, both locally and systemically. One serious adverse event occurred in one patient (multiple bone fractures due to a traffic accident) which was not considered to be related to the study medication. The most frequently observed adverse events with a suspected study drug relationship were of mild to severe intensity and consisted of application site burning, application site reactions, pruritus and dry skin (listed in descending frequency). Two patients discontinued the study due to adverse events; one patient due to severe pruritus, burning at the application site, and nervousness, and one patient due to worsening of pigmentation disorders (post-inflammatory hypo-pigmentation).
The investigator suspected these 4 adverse events to be study drug related. There were no clinically relevant changes in physical examination, vital signs or laboratory parameters observed during the study. In general, the good tolerability of the 1% pimecrolimus cream in the present study was in line with the good tolerability observed in a previous short-term pharmacokinetic study(3).

**Efficacy**

Interpretation of the efficacy data from this pharmacokinetic study was limited due to the open-label, non-controlled study design and because the evaluations were only performed at the visit days. For the overall evaluation of dermatitis, the investigator and patient rated similarly during the study, except that after 1 week treatment the patients rated better compared to the investigator. According to the investigator's judgement, 60% of the patients had their eczema cleared by at least 50% at their end-of-study evaluation compared to baseline, 35% had their eczema cleared by less than 50%, and one patient had worsened during the study. These observations were in line with the results of a long term double-blind efficacy study [data on file, Novartis Pharma]. The mean EASI scores at baseline were similar for both the ITT (with LOCF) and PUT population. At the month 6 visit, the mean EASI score was lower compared to baseline and similar for both populations. At the month 12 visit, the mean EASI score remained stable for the ITT population (with LOCF), whereas it further decreased for the PUT population, indicating that patients with less improvement discontinued the study between month 6 and month 12 of study treatment. The mean EASI change from baseline was stable after 6 and 12 months of treatment for both populations. However, the level of disease improvement was consistently better for the PUT population indicating that the discontinuations due to unsatisfactory therapeutic effect occurred mainly during the first 6 months of treatment. These results are very similar to the results in a long term double-blind efficacy study. A large proportion of the patients (55%) discontinued the treatment due to unsatisfactory therapeutic effect. These subjects had a greater disease severity as represented by a higher percentage of patients (18%) with an EASI > 25 at baseline compared to the other patients (6%). Most of the patients discontinued after the first 1 to 3 months.

The restricted use of second-line therapy for flares not well controlled by the study medication contributed to the patient's decision to discontinue participation in the study.
Chapter 6

CONCLUSIONS

In patients with extensive atopic dermatitis lesions (up to 61.5% of body surface area affected at baseline) treated twice daily with 1% pimecrolimus cream for up to 12 months, blood concentrations of pimecrolimus were consistently low. There was no systemic accumulation over the treatment period of up to 12 months. There was no evidence for increases in blood concentrations in patients with larger areas of body surface under treatment. Pimecrolimus FMF 1% cream applied twice daily for up to 12 months showed a good local and systemic tolerability. The efficacy data in this study were comparable to the current experience with the 1% pimecrolimus cream in the indication atopic dermatitis.

REFERENCES


