CHAPTER 3

Studies concerning new therapies

3.1 Ranitidine does not affect psoriasis: A multicenter, double-blind, placebo-controlled study

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Abstract

\textbf{Background:} Data from open studies suggested that ranitidine has a beneficial effect on psoriasis and is well tolerated.

\textbf{Objective:} Our purpose was to determine the effectiveness of ranitidine in a 24-week, multicenter, double-blind, placebo-controlled, dose-comparing study of 201 patients with psoriasis.

\textbf{Methods:} Patients with moderate to severe psoriasis who had stopped systemic antipsoriatic therapy, including PUVA and UVB, for at least 10 weeks were included. After a washout period of 2 weeks, patients were randomly allocated to use either ranitidine, 150 mg twice a day; ranitidine, 300 mg twice a day; or placebo for up to 24 weeks. Assessment with the Psoriasis Area and Severity Index was performed at weeks 3, 6, 9, 12, 18 and 24 after randomization. Reduction of the Psoriasis Area and Severity Index by 70\% at the completion of the study was considered a treatment success.

\textbf{Results:} The success rates at week 24 in the 300 mg, 600 mg and placebo groups were 11\%, 5\%, and 12\%, respectively. No significant differences were observed between the three treatment groups at any stage of the study.

\textbf{Conclusions:} This study provides strong evidence that ranitidine does not affect the skin disease in patients with psoriasis.

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The cause of psoriasis is unknown, but there is evidence that immunologic mechanisms are important in association with a genetic component and external stimuli (e.g. medication, infection, stress). Many topical and systemic therapies are available, but none is curative and all have side-effects. A few publications reported the beneficial effect of histamine antagonists in psoriasis. These drugs have a well documented record of safety with long-term use. However, other publications claimed a worsening effect of H2 antagonists in psoriasis. Witkamp et al. studied these reports and concluded that positive results with H2 antagonists were found in patients who were treated for at least 16 weeks. In an open prospective study with ranitidine for 16 weeks in 20 patients with moderate to severe psoriasis, they found that 65% of patients responded. In these responders a mean decrease of disease activity by 67% was observed. It was also noted that some clearing of psoriasis was heralded by a worsening. The postulated mechanism was a delayed immunosuppressive effect of ranitidine caused by partial blockade of CD8+ cells and an increased histamine production from positive feedback mechanisms. We performed a multicenter, double-blind, placebo-controlled, dose-comparing study in 201 patients with chronic psoriasis to study the effects of treatment with ranitidine beyond 16 weeks.

Patients and methods

Patients
Eligible for the study were men and women with at least 1 year of moderate to severe plaque-type or guttate psoriasis (Psoriasis Area and Severity Index (PASI) between 12 and 20). Patients were excluded if they used medication known or suspected to influence the course of psoriasis (e.g. -blockers, chloroquine), or if they used (or expected to use) an anti-ulcer medication. Patients with conditions interfering with the absorption of ranitidine (i.e. severe liver or renal impairment, malabsorption syndrome, or bodyweight below 50 kg or above 110 kg) were also excluded. Patients stopped systemic antipsoriatic therapy, including PUVA and UVB, at least 10 weeks before entry into the study. All patients gave written informed consent before entering the study.

Study design
All antipsoriatic treatment was discontinued for the duration of the study. Throughout the study (including the washout period) patients were free to use a standardized emollient. After a treatment-free washout period of 2 weeks, patients were randomly allocated to take ranitidine, 150 mg twice a day; ranitidine, 300 mg twice a day; or matching placebo for up to 24 weeks. All study tablets were of identical appearance and taken at breakfast and at bedtime. Visits were scheduled 3, 6, 9, 12, 18, and 24 weeks after randomization. Patients were free to leave the study at all times and, for ethical reasons, were invited to reconsider their participation in the absence of a beneficial effect after 9 weeks of treatment. Disease activity was assessed at all visits by the PASI as well as by the change in overall disease activity compared with the previous visit, according to the patient and the investigator.
The study was performed according to European guidelines for Good Clinical Practice, and was approved by the Ethics Committees of all participating centres.

**Statistical analysis**

Treatment success was defined as a completion of 24 weeks of treatment with a decrease in PASI of at least 70% compared with the initial visit. Secondary outcome features were the proportion of treatment success at weeks 9 and 12. Sample size estimation was performed with a success rate not exceeding 15% in the placebo arm. The power of this study was 80% with a significance level of 5%. All analyses were performed on an intention-to-treat basis. The statistical software SAS (SAS Institutes, Cary, N.C., USA) was used for all statistical analyses.

**Results**

**Patients**

Between October 1992 and December 1993, 202 patients were randomly allocated to one of the three treatment groups. The mean age in the 150 mg ranitidine, 300 mg ranitidine, and placebo groups was 44 ± 13.6 years, 48 ± 13.5 years, and 47 ± 15.3 years, respectively; the mean duration of disease was 20 ± 11.9 years, 25 ± 15.6 years, and 21 ± 14.9 years, respectively; and the PASI at entry was 16 ± 3.4, 16 ± 4.2, and 16 ± 3.0, respectively. One patient assigned to receive 150 mg ranitidine twice a day was found to be pregnant before she had taken any study tablets. She was withdrawn from the study, and was not included in the analyses.

After 9 weeks of treatment, 32% of the patients randomly selected to receive placebo had left the study, compared to 35% in the 300 mg ranitidine group, and 42% in the 600 mg ranitidine group. Of 66 patients randomly selected to receive 600 mg of ranitidine, 24 (36%) completed the 24 weeks treatment period, compared to 39% in the 300 mg group, and 26% of the patients randomly allocated to the placebo group.

**Efficacy**

The proportion of patients with a PASI reduction of 70% or more after 24 weeks of treatment, compared with baseline, was 12% in the placebo group, 11% in the 150 mg ranitidine group, and 5% in the 300 mg ranitidine group \((p = 0.32)\). Statistical differences between the treatment groups could not be demonstrated at any stage of the study.

**Drop outs**

Discontinuation of treatment was almost always because of lack of efficacy, but nine patients discontinued because of adverse events (e.g. other medical conditions, severe exanthema thought to be related to study medication, worsening of psoriasis, pruritus) and three patients because of protocol violation.
**Discussion**

Because of inconsistent reports in literature about the effects of H$_2$-antagonists in patients with psoriasis, an open prospective study was performed and showed promising results. The results of a placebo-controlled study with cimetidine, in contrast, suggested an adverse effect of cimetidine in psoriasis. Another open study with ranitidine also showed a beneficial effect in 11 of 20 patients. The results of the present study provided strong evidence that ranitidine has neither a beneficial nor a worsening effect on psoriasis. Differences between patient groups in initial disease activity were not observed. After 9 weeks, patients not experiencing any benefit from the medication were informed of the possibility to leave the study. This could have made patients, experiencing a ranitidine-induced temporary worsening leave the study prematurely. However, the proportion of patients leaving the study after nine and twelve weeks was the same for all treatment groups.

In this study the number of spontaneous remissions was highest in the placebo group and proves the importance of a control group. Although we concluded that ranitidine was ineffective, it is remarkable that 9% of all patients had a reduction in PASI of more than 70%. A possible explanation is the use of an emollient throughout the study. Because scaling is one of the features scored in the PASI, the use of emollients does influence results. Furthermore, the natural course of psoriasis is unpredictable, as is seen in this study.

Psoriasis is not an indication for ranitidine treatment, and having psoriasis is also not a contraindication for ranitidine treatment.

**Co-workers at participating centers**

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References

Studies concerning new therapies

Discussion

Randomized prospective studies have demonstrated that TAC significantly increased survival in patients with metastatic, an open prospective study was performed to evaluate the potential for survival benefit of TAC in patients with metastatic disease. In the study, patients were randomized to either TAC or standard chemotherapy. No significant differences were observed in overall survival or disease-specific survival between the two groups. The results of this study suggest that TAC may not offer a survival advantage over standard chemotherapy for patients with metastatic disease.
3.2 Efficacy and tolerability of multiple dose SDZ IMM 125 in patients with severe psoriasis

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Abstract

Although cyclosporine A is effective in immunosuppression following organ transplantation and in the treatment of psoriasis, its use is limited by its side-effects, notably impaired renal function and hypertension. As SDZ IMM 125, a new derivative of the cyclosporine family, showed considerable immunosuppressive activity in experimental studies, with less effect on renal function, it was considered a potential successor to cyclosporine for both indications. In this multicentre, double-blind, placebo-controlled study, the efficacy and tolerability of 40, 100, 200 and 400 mg SDZ IMM 125 daily were studied in 59 patients with psoriasis. Patients were followed for a period of 5 weeks (4 weeks treatment, and 1 week post-treatment observation). A dose dependent effect of SDZ IMM 125 was observed. A significant correlation was found between the dose of SDZ IMM 125 and changes in the sum of severity scores of 3 indicator plaques. There was a significant decrease in the body surface affected by psoriasis in the 400-mg group (P<0.01), whereas a decrease of the global psoriasis severity was observed in the 200-mg (P<0.01) and the 400-mg groups (P<0.001). No serious adverse events occurred during the 4 weeks of treatment. Three patients discontinued treatment because of adverse events (1 sore throat, 2 influenza). Clinical adverse events were similar to those reported with cyclosporine, the most frequent being gastrointestinal disturbances. Estimation of renal function indices showed that increase from baseline values were dose-dependent and appeared to be similar to those seen with cyclosporine. Changes in liver function tests showed a clearcut dose-dependent increase of some liver enzymes, principally alanine aminotransferase (ALAT). SDZ IMM 125 is effective in clearing psoriasis. However, long-term studies comparing efficacy and safety of SDZ IMM 125 and cyclosporine must be performed, to determine whether SDZ IMM 125 has a better risk-benefit ratio than cyclosporine.

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Methotrexate,\textsuperscript{1,2} acitretin,\textsuperscript{3-5} photochemotherapy,\textsuperscript{6-8} and cyclosporine (CyA)\textsuperscript{9-11} are all effective in controlling severe psoriasis, but they have potential side-effects which limit their long-term use.\textsuperscript{12-14} CyA has proved to be a very effective drug in the treatment of severe psoriasis, even in cases in which other treatments have failed,\textsuperscript{15} but its use is restricted by its side-effects,\textsuperscript{16} notably on kidney function and blood pressure.\textsuperscript{17} Hence, the development of a cyclosporine derivative with at least the same immunosuppressive potency as CyA, but with a better safety profile, is potentially of great clinical importance. SDZ IMM 125, a new derivative of the cyclosporine family, was considered a good candidate to achieve this goal. SDZ IMM 125 is the hydroxyethyl derivative of D-serine-cyclosporine. In experimental studies, the immunosuppressive activity of SDZ IMM 125 was at least equivalent to that of CyA, without cytostatic or cytotoxic effects. It proved to have a similar ability to suppress production of lymphokines.\textsuperscript{18} In animal models of transplantation and autoimmune diseases, SDZ IMM 125 showed efficacy equal to that of CyA,\textsuperscript{18} and was better tolerated especially with regard to renal function.\textsuperscript{19} In a double-blind, placebo-controlled, single-dose tolerability study with healthy volunteers, dose levels up to 800 mg were investigated (Sandoz AG, Basle, data on file). An increase in transaminases was observed in three of six volunteers after administration of 600 mg and in two of six volunteers after 800 mg. The dose of 400 mg SDZ IMM 125 had been identified as the maximum tolerated dose, and was selected as the highest dose level. The aim of the present multiple-dose study was to investigate the efficacy and tolerability of SDZ IMM 125 administered for 4 weeks up to a dose of 400 mg daily, in patients with severe psoriasis, in whom the use of an immunosuppressant was appropriate.\textsuperscript{20,21}

**Methods**

**Study design**

This was a placebo-controlled, double-blind, multicentre cohort study, with escalating dose levels, to assess the efficacy and tolerability of SDZ IMM 125 in patients suffering from psoriasis. Prior to recruitment, patients were screened for inclusion and exclusion criteria, for previous treatments, duration of psoriasis, overall response to prior medications and standard demographic values. Four different dose levels of SDZ IMM 125 were studied consecutively in ascending order of magnitude: 40, 100, 200 and 400 mg/day. The patients were randomized for each dose group in blocks of 4 patients, with 3 patients receiving study medication and one patient receiving placebo. Study duration for each patient was a maximum of 5 weeks, including a treatment period of 4 weeks and a 1-week follow-up period after stopping treatment. Individual patients could only be included in one dose group. Data on tolerability were analysed for each dose level. Tolerability was based on an assessment of subjective adverse events and clinically relevant abnormalities in vital signs and laboratory parameters, which were defined by the study protocol.

The study was initiated with the 40-mg group. If the dose was well tolerated, and not more than 2 patients had experienced a clinically relevant adverse event, the next dose increment was tested. The same procedure was followed
up to the highest dose level. In the event of a clinically relevant abnormality, the administration of the drug to that patient was to be discontinued. The study was performed according to good clinical practice guidelines as laid down by the U.S. Code of Federal Regulations dealing with clinical studies\textsuperscript{22} and the declaration of Helsinki,\textsuperscript{23} and informed consent was obtained from all participating patients.

\textbf{Patient population}

Patients with severe psoriasis, aged between 18 and 65 years, in whom conventional therapy was ineffective or inappropriate, were included. It was a requirement that the extent or severity of the psoriasis justified the use of an immunosuppressive drug equipotent to CyA. Female patients had to use medically approved birth-control methods, and have a negative pregnancy test. Patients with one or more of the following conditions were excluded: erythrodermic psoriasis; presence or history of malignancy, lymphoproliferative syndrome, clinically relevant allergy, severe adverse reactions or hypersensitivity to any drug; acute uncontrolled infection; any condition which might interfere with the bioavailability of the drug (including obesity); significant coexisting hepatic, renal, cardiovascular, neurological or psychiatric disease; uncontrolled hypertension (defined as blood pressure readings of 160 mmHg systolic or 95 mmHg diastolic or higher), and baseline values 25\% above the upper limit of normal for haematological parameters, liver function tests, urea and creatinine. Patients who had taken any investigational drug within 3 months prior to the study, or any drug metabolism-inducing or inhibiting agents, CyA, methotrexate, retinoids, PUVA or systemic corticosteroids within 2 weeks prior to the study were excluded.

\textbf{Treatment regimen and follow-up}

SDZ IMM 125 was to be taken in two separate daily doses. No change in study medication was allowed. A patient who neglected to take SDZ IMM 125 for more than 2 days was to be withdrawn from the study. During treatment with SDZ IMM 125, no concomitant (antipsoriatic) medication was allowed, except emollients. During the 1 week post-treatment period, only topical antipsoriatic treatment was allowed. If an unauthorized medication had to be administered, the test medication was immediately discontinued and the patient entered the follow-up period of 1 week. Eight clinical evaluations were carried out: at screening, at baseline, 3 days after the start of treatment, and then at weekly intervals. Additional post-treatment evaluations were performed in the event of clinically relevant abnormalities or serious adverse events.

\textbf{Efficacy and safety evaluation}

Three indicator psoriatic plaques were selected for the assessment of treatment efficacy. One plaque had to be mild or recently developed (plaque A), a second had to be moderate (plaque B), and the third had to be severe or chronic (plaque C). The severity of these three indicator lesions was judged by means of a 7-point scale (1, absent; 2, trace; 3, mild; 4, mild-moderate; 5, moderate;
6, moderate-severe; 7, severe). The total body surface affected by psoriasis was recorded according to the rule-of-nines. A global evaluation of the current status of the psoriasis was performed, also using a seven-point scale. At the end of the study, an overall evaluation was performed by the investigator and the patient, comparing the patient's state with the baseline evaluation, using a five-point scale (1, very good; 2, good; 3, moderate; 4, slight; 5, none). Adverse events were spontaneously reported, were elicited by questions from the investigator, or were detected by physical examination. They were recorded at each visit, together with the time of occurrence and of resolution, the severity, the relation to treatment, and the course. The severity was graded on a three-point scale, comprising mild, moderate and severe. Physical examination and electrocardiograms were performed at baseline and at the end of week 4. Standing and supine blood pressure and radial pulse rate, oral temperature and body weight were recorded at each visit. Standard haematological investigations were carried out, with the patient in a fasting state, at all visits. All concomitant medications were recorded at every visit.

**Statistical methods**

Descriptive statistics were given for all quantitative demographic and background variables. Significance tests for homogeneity were performed. Two-dimensional before-after plots were presented for each of the efficacy variables, representing a patient's data as a point in the plane, whose first coordinate is the value at entry, the second coordinate the value at the end of treatment. Point estimates and $95\%$ confidence intervals for the location parameter based on Wilcoxon matched-pairs signed rank statistics were provided for the data at entry, at the end of treatment and also for their difference. This was carried out separately for each dose group. When a dose relationship became apparent, this was further investigated, by regression analysis. Safety was evaluated in terms of vital signs, physical examination, laboratory analysis, ECG, infections and other adverse events. Clinically relevant abnormalities were identified and newly occurring abnormalities were assessed with regard to whether they were drug-related or not. For haematology, biochemistry and urine examination, the number of deviations from within the normal range to values outside the normal range were tabulated. Similar analyses were done to check for (increasing and decreasing) trends. $P$-values of non-parametric tests were used for descriptive purposes. Laboratory parameters whose course during the trial appeared to be influenced by the test medication were further analysed by regression with time and dose. Laboratory parameters showing an unusual behaviour were analysed further by descriptive correlation analyses, such as scatter plots. Infections and adverse events were listed and sorted according to type and patient. Incidence rates were calculated to compare the dose groups. For each dose group, incidence rates were calculated for the occurrence of clinically relevant abnormalities. In order to identify both pharmacological effects and idiosyncratic reactions, all clinical and laboratory parameters were analysed as mean values and as the incidence and severity of abnormal individual values versus time and dose.
Table 1. Premature treatment discontinuations

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>Treatment</th>
<th>day</th>
<th>Reason</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>12</td>
<td>AE</td>
<td>Rhinitis*</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>7</td>
<td>PV</td>
<td>Uncooperativeness</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>15</td>
<td>PV</td>
<td>Delayed exclusion</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>15</td>
<td>PV</td>
<td>Delayed exclusion</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>15</td>
<td>PV</td>
<td>Delayed exclusion</td>
<td></td>
</tr>
<tr>
<td>400</td>
<td>11</td>
<td>AE</td>
<td>Diarrhoea, fever*</td>
<td></td>
</tr>
<tr>
<td>400</td>
<td>10</td>
<td>AE</td>
<td>High fever</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td>Inefficacy</td>
<td>Worsening psoriasis</td>
<td></td>
</tr>
</tbody>
</table>

AE, adverse event; PV, protocol violation.
*Rated as unrelated to study medication by the investigator.

Results

Patient population

Forty-one males and 18 females, with a mean age of 39 years, were recruited. One to three randomization was achieved within each treatment group (active versus placebo in 40-mg/day group, 9:3; in 100-mg/day group, 10:4; in 200-mg/day group, 12:4; in 400-mg/day group, 12:4). On average, the global severity of the psoriasis was rated "moderately severe" (median score of 6). The total body surface affected by psoriasis was 26 ± 20%. Half of the population had an affected area of between 10 and 40% of the body surface. The average disease duration was 17 years. Forty-two percent of the patients had a disease duration of 10 to 19 years. One or more systemic antipsoriatic therapies had been previously administered to 68% percent of the patients (n = 40). Five patients had received methotrexate previously. None of the 3 patients who were delayed exclusions due to abnormal liver tests had received methotrexate previously.

Eight patients were withdrawn from the study prematurely: 3 because of adverse reactions (1 on 40 mg, 2 on 400 mg), 4 because of protocol violation (1 on 40 mg, 2 on 100 mg, 1 on 200 mg) and 1 because of treatment failure (table 1). Contraindicated medications were used by 3 patients (topical steroids, flunitrazepam and loratadine). Authorized medications (topical agents, hormonal contraceptives, paracetamol and derivatives) were used by a total of 21 patients, most frequently topical salicylic acid (5 patients) and paracetamol (7 patients).
Table 2. Efficacy parameters; baseline and absolute changes at week 4

<table>
<thead>
<tr>
<th>Group</th>
<th>40mg/day</th>
<th>100mg/day</th>
<th>200mg/day</th>
<th>400mg/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plaque A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.0</td>
<td>4.5</td>
<td>4.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Change</td>
<td>-0.5</td>
<td>0.1</td>
<td>-0.8</td>
<td>-1.2</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Plaque B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.0</td>
<td>5.5</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Change</td>
<td>-0.5</td>
<td>-0.5</td>
<td>-1.5*</td>
<td>-2.1*</td>
<td>-0.2</td>
</tr>
<tr>
<td><strong>Plaque C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.0</td>
<td>6.0**</td>
<td>7.0</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Change</td>
<td>-0.5</td>
<td>-0.9</td>
<td>-1.4*</td>
<td>-2.5*</td>
<td>-0.4</td>
</tr>
<tr>
<td><strong>Percent body surface</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean±SD)</td>
<td>35±17</td>
<td>35±17</td>
<td>19±14</td>
<td>24±23</td>
<td>21±22</td>
</tr>
<tr>
<td>Change</td>
<td>-3±8</td>
<td>-4±11</td>
<td>0±4</td>
<td>-8±8*</td>
<td>1±5</td>
</tr>
</tbody>
</table>

Severity of the indicator lesion: 1, absent; 2, trace; 3, mild; 4, mild-moderate; 5, moderate; 6, moderate severe; 7, severe.

* P ≤ 0.01, **P ≤ 0.05, by the Sign test; intention to treat analysis.

**Efficacy**

The absolute change in the severity of indicator lesions was greater with respect to plaques B and C (moderate and severe) than for plaque A (mild or recently developed). For plaque C, a significant decrease in the severity index at week 4 was detected at doses of 100, 200 and 400 mg (table 2). For plaque B, the improvement was less than for plaque C, but still significant in the 200- and 400-mg groups. For plaque A, the improvement did not reach statistical significance. A significant correlation (r = 0.61, P = 0.001) was found between the dose of SDZ IMM 125 and the changes in the sum of the severity of the 3 indicator plaques. The treatment groups differed in the percentage of body surface affected by psoriasis at baseline. The difference ranged from 19% in the 200-mg group to 35% in the 40- and 100-mg groups. The decrease in body surface area affected was significant at week 4 in the 400-mg group. No significant change in the psoriasis global severity evaluation was detected at week 4 in the 40- and 100-mg groups.

**Global evaluation and overall evaluation**

A significant decrease of the severity by 1.0 grade (P ≤ 0.01) was observed in the 200-mg group, and a decrease by 2.5 grade (P ≤ 0.001) in the 400-mg group (table 3). At the end of the treatment period, 42% of the patients in the 200-
mg group and 82% in the 400-mg group had improved to an extent that their psoriasis was rated as mild or totally clear at week 4. The percentage of patients in whom the efficacy was rated as good or very good by the investigator after 4 weeks' treatment increased in parallel with the dose (7% on placebo, 0% on 40 mg, 40% on 100 mg, 62% on 200 mg, and 83% on 400 mg). Overall, the patients' evaluations of efficacy were similar to those of the investigators.

Safety

Data for safety on week 4 were available for 50 patients, as 8 patients had already discontinued the study and one patient in the 400-mg group missed the week 4 visit. The post-treatment visit was missed by two patients, one in the placebo group and one in the 40-mg group.

No serious adverse events (according to WHO definition) occurred during the study. Three patients discontinued the study because of minor infections: upper respiratory tract infection in one patient on 40 mg, diarrhoea and fever in one patient on 400 mg, and influenza-like symptoms in another patient on 400 mg. In the last mentioned case, treatment was discontinued on the basis of the study protocol (fever >39°C); in the two other cases, the reason for discontinuation was the need for concomitant medication.

A total of 77 clinical adverse events were reported by 33 out of 59 patients. One was recorded as severe (headache in the 100-mg group); the relation to study medication was rated as remote by the investigator.

The incidence of adverse events was higher in patients who received SDZ IMM 125 than in those who received placebo, especially in the 400 mg group, in which 83% of the patients experienced adverse events at a rate of 2.8 events per patient. In the majority of patients, the adverse events were considered to be mild, irrespective of the treatment group. A relationship between the adverse events and study medication was considered absent or remote in 42 events (55%), possible in 30 (39%), probable in four, and definite in one (mild dyspepsia). More adverse events were considered possibly related to the drug in the 200-mg and 400-mg group than in the other groups.

The most frequent clinical adverse events were abdominal disturbances, headache, paresthesia, and fever (table 4). Abdominal disturbances occurred

<table>
<thead>
<tr>
<th>Table 3. Global psoriasis severity; absolute changes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Baseline (median)</td>
</tr>
<tr>
<td>Change</td>
</tr>
</tbody>
</table>

Global evaluation of psoriasis: 1, absent; 2, trace; 3, mild; 4, mild-moderate; 5, moderate; 6, moderate-severe; 7, severe.

* p≤0.01, ** p≤0.001, by the Sign test; intention to treat analysis
### Table 4. Number of adverse events (AE) by organ system

<table>
<thead>
<tr>
<th>Group</th>
<th>40</th>
<th>100</th>
<th>200</th>
<th>400</th>
<th>Placebo</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>10</td>
<td>13</td>
<td>12</td>
<td>15</td>
<td>59</td>
</tr>
<tr>
<td>No. of patients with AEs</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>No. of AEs</td>
<td>9</td>
<td>11</td>
<td>20</td>
<td>28</td>
<td>9</td>
<td>77</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>2</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>-</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Gum hypertrophy</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Bone/joints</td>
<td>-</td>
<td>(2)</td>
<td>-</td>
<td>-</td>
<td>(2)</td>
<td>(2)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>4</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Genitalia</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Various</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Infections (events/patient)</td>
<td>6/3</td>
<td>1/1</td>
<td>2/2</td>
<td>3/3</td>
<td>4/3</td>
<td>16/12</td>
</tr>
<tr>
<td>Upper resp. tract</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Influenza-like</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Undefined</td>
<td></td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate the sum of the adverse events affecting the organ system.

In 2 patients on 100mg and 3 patients in each of the 200-mg and 400-mg groups, but not in the placebo and 40-mg groups. The severity was mild to moderate, and the relation to the drug varied from remote to definite. Headaches occurred more frequently in the placebo group than in patients taking SDZ IMM 125, and it was considered that they were unlikely to be due to the study medication. Paresthesias were recorded as mild in all patients who complained of this symptom, primarily in the 400-mg group. Paresthesia occurred either intermittently or as a single episode. Other neurological adverse events included tremor \( n = 2 \), dizziness, tinnitus, hyperkinesia and psychiatric disorders.
A total of 16 infectious episodes occurred in 12 patients. The number of infections was not greater in the 400-mg group than in those on placebo. Out of the 16 infectious episodes, 4 were considered moderate, all in the 40-mg group; all other episodes were recorded as mild. In 5 patients clinically relevant abnormalities of vital signs were detected [1 on 40mg (diastolic blood pressure = 111 mmHg), 2 on 400mg (pulse = 47 beats per minute, weight increase 7.3%) and two on placebo (pulse = 38 and 50 beats per minute)]. No noticeable abnormalities were detected on the remainder of the physical examination in comparison with baseline.
No significant changes in systolic or diastolic blood pressure were detected. Only modest increases of creatinine, urea and uric acid were observed in patients taking 200 and 400mg. The abnormality mainly affected blood urea (table 5). A significant rise of urea was observed in the 400-mg group ($P<0.05$). Changes in urea were not associated with changes in serum creatinine. In the 200-mg group, a rise by $11 \pm 10\%$ of creatinine was detected at week 4. In the 400-mg group, creatinine showed a trend for an increased level at weeks 2 and 4. In the 200 and 400-mg groups, a significant rise in urine acid of $17 \pm 15\%$ and $26 \pm 14\%$, respectively was observed at week 4. A slight decrease in magnesium and an increase in phosphorus, with no change in potassium was detected. There was a clearcut dose-dependent increase of some liver enzymes, mainly alanine aminotransferase (ALAT), which rose on average $116 \pm 144\%$ in the 400-mg group, and to a lesser extent aspartate aminotransferase (ASAT) and gamma-glutamyl transpeptidase (GGT). In the 200-mg group, a rise of 46% in ALAT was detected as early as day 3, and increased to 119% at week 4. In the 400-mg group a rise of 118% was detected at day 3, without a clearcut progression at subsequent visits. Five patients, 1 in the 100-mg group, one in the 200-mg group and three in the 400-mg group, had an ALAT or ASAT level during treatment which exceeded three times the upper limit of normal. In the 200- and 400-mg groups, a slight but significant rise in alkaline phosphatase was detected at week 4. These were the only clinically relevant changes in laboratory parameters observed, apart from a rise in alpha-amylase in two patients.

**Post treatment observation**
Clinically relevant abnormalities which had emerged during treatment resolved after treatment cessation. All abnormalities in blood chemistry, including clinically relevant abnormalities, were reversible, although full reversibility was not achieved in all patients one week after the treatment was stopped. A significant rise in mean uric acid at the end of the post-treatment observation period, compared with baseline, was observed in the 400-mg group ($13 \pm 19\%$, $P<0.05$). All increases in liver enzymes, including ALAT and ASAT returned to normal, and did not differ significantly from baseline values. Changes in cholesterol were reversible upon treatment discontinuation. No clinically relevant abnormality was present at week 5.

**Discussion**
In this study, we investigated the efficacy of SDZ IMM 125, administered for 4 weeks, up to a dose of 400 mg daily. As this is the first study in which chronic dosage of SDZ IMM 125 in humans has been evaluated, the starting dose was low (40mg/day) as compared to placebo. After careful monitoring and evaluation of vital signs, laboratory parameters and adverse events during 4 weeks' treatment with this low dose, patients were subsequently treated with a higher dose. It was decided to assess the efficacy of treatment by evaluating 3 individual plaques which differed in severity, as well as by rating overall activity of the psoriasis. The extent of the disease was determined by the rule-of-nines. The
Studies concerning new therapies

CHAPTER 3

classic Psoriasis Area and Severity Index (PASI)\textsuperscript{24} was not measured, because the study population was not restricted to chronic diffuse plaque-type psoriasis, which is best evaluated by the PASI. Particularly when the PASI is lower than 10, its reliability decreases, as the area involved is an important factor in the calculation of the PASI. Overall, the global psoriasis severity was related to the percentage of body surface area affected by the disease. Nevertheless, in 14 patients in whom the affected area was less than 10\% of the body surface, the global psoriasis severity was still rated as moderate (score 5, median), indicating that in some patients the disease severity was not attributable to the extent of involvement, but to recalcitrant localized disease. This is not fully reflected by the PASI. The efficacy of SDZ IMM 125 was clearly demonstrated, especially in the 200- and 400-mg groups. In these two groups, there was a significant reduction in the severity of the indicator lesions for the moderate and severe plaques. In the 400-mg group, the severity of the most severe plaque was reduced from moderate-severe at baseline to mild and mild-moderate at week 4. A reduction of 43\% was achieved in the sum of plaques A, B and C, which is comparable with results achieved with CyA given for 4 weeks.\textsuperscript{9} The percentage of body surface affected by psoriasis was reduced significantly in the 400-mg group. Assessment of this parameter should be continued during treatment for periods longer than 4 weeks, as the area affected by psoriasis is the last parameter to change after resolution of erythema and scaling during antipsoriatic treatment. In studies with CyA, it has been established that optimal efficacy is reached after 12 to 16 weeks. Global severity assessment changed from moderate-severe at baseline to moderate in the 200-mg group and to mild in the 400-mg group, at week 4. Three patients stopped treatment prematurely because of an adverse event, more as a consequence of protocol requirements than because of the adverse event itself. Clinical adverse events were similar to those reported with CyA. No substantial change in vital signs, especially blood pressure, was observed. A minor increase in body weight, in the absence of oedema, was noted in the 400-mg group. The clinical relevance of this finding remains to be investigated. The main adverse event was a dose-dependent rise in liver enzymes, which predominantly affected ALAT, but also, to a lesser extent, ASAT and GGT, and minimally involved alkaline phosphatase. The abnormalities in ALAT and ASAT were not associated with any clinical symptoms. The rise in ALAT was already evident at the first visit, after 3 days of treatment (up to 118\% in the 400-mg group), was stable overall during treatment, and was reversible after treatment had stopped. Reversibility after one week was complete or almost complete up to the dose of 200 mg, but was incomplete on 400 mg, although the changes in ALAT at the post-treatment visit were clinically irrelevant. More than 50\% of the patients in the 200- and 400-mg groups had a rise of ALAT above the upper limit of normal. Increases of ASAT or ALAT above 3 times the upper limit of normal were not sustained, and occurred in one patient in the 100-mg group, one patient in the 200-mg group and 3 patients in the 400-mg group. ALAT was the predominant liver enzyme affected. The occurrence of an abnormal ASAT was never observed if the
ALAT was normal. However, the reciprocal was not the case. A significant correlation was found between the dose of SDZ IMM 125 in mg/day (as well as when expressed as mg/kg/day) and the percentage rise in ALAT (Pearson's correlation coefficient). This correlation was not found for ASAT.

The experience with CyA in psoriasis and other autoimmune diseases has shown that renal dysfunction is an important adverse effect, and that a sustained rise in serum creatinine of 30% or more above baseline should be avoided. Therefore, renal function was monitored in more detail than routine laboratory parameters.

Modest increases in serum creatinine, urea and uric acid were observed in the 200- and 400-mg groups. A trend for an increase in urea and creatinine levels over the 4-week treatment period was noted, and these levels may not have reached their plateau at week 4. These abnormalities were reversible, although full reversibility was not achieved in all patients 1 week after stopping treatment. In the 200-mg group, a significant rise of 13% in creatinine was detected at week 3 (P ≤ 0.01). The values at day 3, week 2 and week 4 were also significantly higher than baseline. This rise in creatinine was reversible after treatment was stopped. In the 400-mg group, a significant rise of 38% (P ≤ 0.05) in urea was observed at week 4. One patient in the 200-mg group and one in the 400-mg group had a rise in creatinine of between 30 and 50%. Two patients had a rise higher than 50%, one in the 40-mg group and one in the 100-mg group. These values returned to normal after stopping treatment. It is known from clinical experience with CyA that calculating the reciprocal of both the rise in urea and creatinine (index of renal function = [creatinine<sub>x</sub>/creatinine<sub>0</sub> + urea<sub>x</sub>/urea<sub>0</sub>] / 2) gives a better estimate of the fall in glomerular filtration rate (GFR) than creatinine or urea taken alone. One of the reasons for this is that the index minimizes the variability of either creatinine or urea measured separately. The results were similar to those observed with either urea or creatinine alone, but were more consistent overall. A trend for dose-dependent and time-dependent increases in the renal function index was observed, but this was reversible on stopping treatment. In one patient in the 400-mg group, the change in renal function index was greater than 50%.

One week after stopping treatment, the levels of some parameters remained above pre-treatment values. However, in no case it was necessary to follow-up a patient for a longer period, as dictated by the protocol if a clinically relevant adverse event occurred.

In summary, this study shows that SDZ IMM 125 has a dose-related beneficial effect on psoriasis. However, the occurrence of abnormal liver function tests and the effect of long-term SDZ IMM 125 on renal function require further evaluation. This study does not allow a comparison between SDZ IMM 125 and CyA with regard to efficacy and the severity of adverse effects, as no CyA control group was included. Hence, long-term comparative studies with CyA should be performed, in order to evaluate further the usefulness of SDZ IMM 125 as an antipsoriatic treatment.
References


3.3 Cyclosporine A micro-emulsion: dose requirements in patients with psoriasis.

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²Department of Research, Novartis Pharma B.V., Arnhem, The Netherlands.

Abstract

Background: The bioavailability of cyclosporine A (CsA) in the first available form is highly variable. Recently a new galenic form, CsA micro-emulsion, has demonstrated a more consistent absorption resulting in a more predictable pharmacokinetic profile. We performed an open prospective study to investigate the use of CsA micro-emulsion, especially the switch to this new formulation, in patients with psoriasis currently treated with a stable dose of CsA.

Study design: Patients had been treated with CsA (2.5-5 mg/kg/day) for at least 3 months with a relevant clinical improvement and no need for dose adjustments in the last three weeks before entry into the study. After a three week pre-conversion period to obtain baseline values all subjects were switched at day 0 to CsA micro-emulsion at a dosage of 66% of their CsA dosage.

Results: Of 24 patients more than 50% (13/24) had a dose 1.0-1.5 mg/kg/day lower than the starting dose after 15 weeks of CsA micro-emulsion treatment. The mean disease severity remained stable during the study, but 4 patients improved. Adverse events were noted but never a reason for drop-outs. CsA micro-emulsion did not show a different side-effect profile compared to CsA.

Conclusion: It has been shown that with a reduction in dose of approximately 20%, patients currently using CsA, can be safely switched to CsA micro-emulsion without changes in psoriasis severity.

Psoriasis is a multifactorial chronic skin disease characterized by inflammation and epidermal hyperplasia within the lesion. Cyclosporine A (CsA) has proved to be a very effective drug in psoriasis, but its use is limited by its potential dose-dependent side-effects, especially on renal function. It has been difficult in the past to achieve a stable drug exposure of patients treated with CsA, as its bioavailability in the first available form (Sandimmune) is highly variable, ranging from 20 to 50% inter- as well as intra-individually. Recently, a new galenic form of CsA has been developed (SandimmuneNeoral). This CsA micro-emulsion has demonstrated a more consistent absorption resulting in a more predictable pharmacokinetic profile. Therefore, it is anticipated that this new formula will allow better control of disease activity and reduce the frequency of unwanted side-effects, related to the often unsuspected high levels of CsA in the blood. In patients responsive to the old CsA formula, the new CsA micro-emulsion has shown to lead to a substantially higher Area Under the Curve (AUC), approximately 50% higher, accompanied by a moderate increase in efficacy. We therefore performed an open, prospective study to investigate the use of CsA micro-emulsion, especially the switch to this new formula, in psoriasis patients currently treated with a stable maintenance dose of CsA. The study aimed to demonstrate that a conversion strategy by which patients on a stable CsA dosage are switched to CsA micro-emulsion at a starting dose of 66% of the pre-study CsA dose, is clinically feasible and does not cause significant tolerability or safety problems.

**Patients and methods**

All patients had a history of generalized chronic plaque-form psoriasis. Patients had been treated with CsA for at least 3 months, leading to relevant clinical improvement, as judged by the investigator. Their CsA dose ranged between 2.5-5 mg/kg/day, with no need for dose adjustments in the three weeks preceding the study. Safety variables (e.g. creatinine, liver enzymes) were within the normal range. After a three week pre-conversion period to obtain baseline values and check of eligibility, all subjects were switched at day 0 to CsA micro-emulsion at a dosage of 66% of their CsA dosage. Disease activity was assessed by the PASI, a global 7-point scale and body surface involved. At three weekly intervals, the dose could be increased if the psoriasis did not respond adequately or decreased if side-effects occurred or worsened. Inadequate response was defined as an increase in global evaluation score by at least 2 points, or deterioration of the PASI by a minimum of 8. A dosage decrease was allowed if serum creatinine increased by 30 to 50% above baseline value, if serum transaminases or alkaline phosphatase levels increased above 3 times the upper limit of normal, if bilirubin levels increased above 2 times the upper limit of normal, if a rise in diastolic blood pressure to 95-110 mmHg could not be adequately reversed with a calcium antagonist or if other intolerable adverse events occurred. Patients were observed for 5 weeks fol-
**Table 1. Dose and correlating cyclosporine A through levels**

<table>
<thead>
<tr>
<th></th>
<th>Dose (range)</th>
<th>Blood level (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>before conversion</td>
<td>3.8 (2.5-5.0)</td>
<td>148 (45-523)</td>
</tr>
<tr>
<td>week 0</td>
<td>2.5 (1.5-3.5)*</td>
<td>176 (20-810)</td>
</tr>
<tr>
<td>week 15</td>
<td>3.0 (2.0-4.5)*</td>
<td>88 (20-168)</td>
</tr>
</tbody>
</table>

* p < 0.001; Dose is given in mg/kg/day, blood level is given in g/l.

Following the conversion. No other concomitant medication that could influence the outcome was allowed from 5 weeks before conversion until the end of the study.

**Results**

**Dose**

A total of 24 patients entered the study. The mean CsA dose before conversion was 3.8 mg/kg/day (range 2.5-5.0 mg). Immediately following conversion the mean CsA micro-emulsion dose was 2.5 mg/kg/day, to end at week 15 at a mean dose of 3.0 mg/kg/day (range 2.0-4.5 mg). Doses and corresponding CsA levels are listed in table 1. Means, standard deviations and maximum of CsA levels were from week 9 onwards much lower than before conversion. Figure 1 shows the number of patients for each difference in dose between weeks -3 and 15. For 7/24 patients the final dose was the same as the starting dose. More than 50% of patients (13/24) had a final dose that was 1.0-1.5 mg/kg/day lower than the starting dose.

**Figure 1.** Difference in dose between CsA and CsA micro-emulsion at the end of the study
**Disease severity**

Since the 7-point global scale is a quantitative measurement, medians are used to express the effects of treatment. Median disease severity on the global scale did not change significantly during the entire study period. In weeks -3, 0, and 3 the median value was 3, in weeks 6, 9, and 12 the median value was 4 and in week 15 the median global score was 3.5. Ten patients had the same global score at week 15 as at week 0, four had a score 1 grade lower, and ten had a higher score. Wilcoxon matched-pairs signed rank-tests gave \( P = 0.49 \) and \( P = 0.32 \) for the comparisons of week -3 and 0 with week 15 respectively.

**Adverse events**

Most adverse events were the subjective paraesthesia and headache. Table 2 shows the changes in creatinine and blood pressure during the study period, as these are the most important ones. Comparison by means of paired t-tests of weeks -3 and 0 with the later assessments only showed a significant difference between creatinine levels at weeks 0 and 3, the latter being marginally lower. All other comparisons showed no statistically significant changes.

**Discussion**

At the start of the study it was presumed on the base of pharmacokinetic studies that the dose of CsA micro-emulsion could be reduced in comparison to the dose originally given with CsA, without any influence on the efficacy. In the pharmacokinetic studies the area under the curve for CsA micro-emulsion was substantially higher.\(^\text{10,11}\) In this study, this hypothesis has been tested in patients with psoriasis. It has been shown that the mean dose of CsA micro-emulsion can be 80% of the dose previously given with CsA, in more than 50% of the individuals. It is also clear from this study that not all patients benefit from the switch to CsA micro-emulsion. This might be explained by the fact

**Table 2. Changes in creatinine (mol/l) and blood pressure (MmHg) during the study period**

<table>
<thead>
<tr>
<th>week</th>
<th>creatinine (mean SD)</th>
<th>systolic BP (mean SD)</th>
<th>diastolic BP (mean SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>87.79 (18.93)</td>
<td>132.7 (17.6)</td>
<td>84.1 (9.1)</td>
</tr>
<tr>
<td>0</td>
<td>88.25 (16.60)*</td>
<td>130.6 (17.7)</td>
<td>83.6 (9.2)</td>
</tr>
<tr>
<td>3</td>
<td>85.12 (16.19)*</td>
<td>131.6 (24.1)</td>
<td>85.5 (13.0)</td>
</tr>
<tr>
<td>6</td>
<td>86.70 (17.73)</td>
<td>133.7 (22.0)</td>
<td>83.7 (10.2)</td>
</tr>
<tr>
<td>9</td>
<td>86.62 (17.57)</td>
<td>133.0 (21.7)</td>
<td>85.1 (10.0)</td>
</tr>
<tr>
<td>12</td>
<td>88.66 (20.49)</td>
<td>129.5 (22.0)</td>
<td>83.8 (9.2)</td>
</tr>
<tr>
<td>15</td>
<td>85.79 (15.87)</td>
<td>133.5 (24.8)</td>
<td>86.9 (9.5)</td>
</tr>
</tbody>
</table>

*\( p=0.46 \)
that CsA has been absorbed poorly in some individuals but not in all. If the patient was already absorbing the old formula very well, the change to CsA micro-emulsion will not bring any further improvement, nor will the dose be influenced. However, if the patient needed high dosages of CsA because of absorption problems, the switch to CsA micro-emulsion will result in better efficacy. These findings together with the findings of Koo et al\textsuperscript{12}, who found a mean decrease of the dose of 10\% with the new CsA micro-emulsion, should have consequences for the currently accepted starting dose of CsA in patients with psoriasis\textsuperscript{13}. Further study is necessary to establish minimum starting dose and maybe also the maximum dose of the CsA micro-emulsion. The two major side-effects of CsA, i.e. hypertension and nephrotoxicity, are thought to be dose dependent and depending on the peak levels of CsA\textsuperscript{14}. As the peak levels of CsA micro-emulsion are much lower than previously with CsA, it is expected that there will be no increase in these side-effects. From this study one cannot clearly predict whether side-effects will increase or decrease because of the better absorption, because we reduced the dose immediately at the beginning of the switch. An increase in the short-term side-effects has not been observed in those patients that eventually needed the same dose of CsA micro-emulsion. As the new formula is already been used in Europe on a large scale and no increase in side-effects has been reported yet, it is not expected that this will be a problem in the future. However, a proper monitoring of patients using CsA micro-emulsion for a longer period is necessary.

In conclusion, CsA micro-emulsion has no adverse effects in our study population, compared to CsA, and has an equal efficacy. More than 50\% of patients formerly using CsA can be switched to CsA micro-emulsion by reducing the dose with approximately 20\%.

In general the short-term side-effects of CsA micro-emulsion do not differ from the known side-effects of CsA.
References


3.4 Systemic tacrolimus (FK506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study

The European FK506 Multicentre Psoriasis Study Group

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Abstract

Background and Design: Fifty patients with severe recalcitrant plaque-type psoriasis were randomized to receive treatment with either oral tacrolimus (FK 506) (n = 27) or placebo (n = 23) for 9 weeks. The two treatment groups were comparable with respect to baseline demographic data. The initial dose was 0.05 mg/kg per day and, in cases of insufficient efficacy, could be increased to 0.10 and 0.15 mg/kg per day at the end of weeks 3 and 6, respectively. Treatment efficacy was based on the percentage reduction in the Psoriasis Area Severity Index compared with baseline data. Patients were defined as responding to therapy if the percentage change in the Psoriasis Area Severity Index from baseline after 3, 6, and 9 weeks was 20% or greater, 45% or greater, and 70% or greater, respectively. Safety was assessed on the basis of all adverse events reported.

Results: At the end of week 9, tacrolimus-treated patients had a significantly greater reduction in the Psoriasis Area Severity Index than did placebo-treated patients (tacrolimus -83, placebo -47; P < 0.02). Similar numbers of patients in both groups responded to therapy at the end of week 3, but at the end of weeks 6 and 9, more tacrolimus-treated patients responded to therapy (week 6: 12 tacrolimus- and 6 placebo-treated patients; week 9: 12 tacrolimus- and 3 placebo-treated patients). Diarrhoea, paraesthesia, and insomnia were the most frequently reported causally related adverse events in the tacrolimus-treated group. All of the reported adverse events were mild or moderate in severity, and all resolved without change in study medication.

Conclusion: Compared with placebo, tacrolimus is efficacious in the treatment of recalcitrant plaque-type psoriasis.

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Psoriasis is believed to be an immunologically mediated disease.\(^1\) Remission of psoriatic lesions has been observed following treatment with cyclosporine (cyclosporine A),\(^2\) which is an immunosuppressant that is normally used in organ transplantation.\(^3\) Tacrolimus (FK506), a novel macrolide lactone, is 10 to 100 times more potent \textit{in vitro} compared with cyclosporine,\(^4\) suggesting that tacrolimus would be at least as successful as cyclosporine in the treatment of recalcitrant plaque-type psoriasis. \textit{In vitro} data have demonstrated that tacrolimus has a strong antiinflammatory activity and interferes with several IgE receptor-mediated processes (e.g., histamine and serotonin release in human skin mast cells and basophils, prostaglandin \(D_2\) synthesis in human skin mast cells, and leukotriene \(C_4\) secretion from human basophils and lung mast cells).\(^5,6\) Similar to cyclosporine, tacrolimus interferes with activated T-cell interleukin-2 messenger RNA production and subsequent protein production of this autologous T-cell growth factor. Of special interest is the down-regulation by tacrolimus of the inflammatory mediator, namely, interleukin-8. Interleukin-8 is a chemokine that is elevated in psoriatic lesions. Interleukin-8 is thought to play a role in the accumulation of neutrophils and activated T cells in the dermis and epidermis.\(^7\) Initial clinical experience has indicated that seven patients had a dramatic resolution of severe plaque-type psoriasis following treatment with tacrolimus.\(^8\) In this article, we document the results of the first placebo-controlled, prospective study that has assessed the efficacy and safety of systemic tacrolimus administered to patients who were suffering from recalcitrant plaque-type psoriasis.

**Patients and Methods**

**Study Design**

This was a phase II, multicentre, randomized, double-blind, placebo-controlled study that was conducted in six centres in four European countries: Germany, Latvia, The Netherlands, and Poland. Patients were randomly assigned within blocks of four to receive treatment with either tacrolimus or placebo for nine weeks. Patients were subsequently followed up for 3 weeks. The study was conducted in accordance with the Declaration of Helsinki (Finland). Approval was obtained from the local ethics committees, and every patient gave written informed consent before participation in the study.

**Patient Selection**

Nonhospitalized male and female patients (age range, 18-70 years) with a diagnosis of moderate to severe recalcitrant psoriasis vulgaris were eligible for the study. Exclusion criteria specified that patients should not have received systemic treatment for 4 weeks or any active topical treatment for 2 weeks before entering the study. Further exclusion criteria included impaired liver, kidney, or heart function; vasculitis; arteritis; a history of pancreatitis or diabetes mellitus; malignant tumor; infection; serious hypersensitivity; or epilepsy. Women who were pregnant or breast-feeding were also excluded from the study.
Table 1. Efficacy and safety parameters

**Efficacy**

Percentage change in PASI* compared with baseline after three, six and nine weeks.

Patients were defined as responding to therapy if the percentage change in PASI from baseline after three weeks was ≥20%, after six weeks ≥45% and after nine weeks ≥70%.

**Safety**

Incidence of all adverse events irrespective of causality to study drug.

Measurement of haematological and biochemical parameters with special attention to renal function and glucose homeostasis.

* PASI indicates Psoriasis Area Severity Index

Change in PASI expected by investigators when using active drug in this indication

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**Study Medication**

Patients who were randomized to treatment with tacrolimus received an initial oral dose of 0.05 mg/kg per day. In the case of insufficient efficacy and the absence of adverse events, the dose could be increased by 0.05 to 0.10 and 0.15 mg/kg per day at the end of weeks 3 and 6, respectively. Whole-blood levels of tacrolimus were measured by an enzyme-linked immunosorbant assay.

**Evaluation of Efficacy and Safety**

The primary efficacy and safety parameters were defined before the study began and are shown in table 1. Patients who responded to therapy were defined according to the percentage change in the Psoriasis Area and Severity Index (PASI). These parameters were agreed on by the participating investigators and, in their opinion, represents the change in the PASI that they would expect to see when using an active drug in this indication. Creatinine clearance was calculated according to the following formula: (140-age [years] x body weight [kg]/plasma creatinine [milligrams per deciliter] x 72.

**Statistical Analysis**

All analyses were of the intent-to-treat population. The percentage change in the PASI from baseline was analyzed by the Wilcoxon-Mann-Whitney test after 3, 6 and 9 weeks. The main target parameter was the percentage change in the PASI after 9 weeks. As no α adjustment was performed, P-values for the percentage change at week 3 and 6 are of a descriptive nature only.
### Table 2. Patient characteristics at baseline*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tacrolimus (FK506) (n=27)</th>
<th>Placebo (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>36.1</td>
<td>45.6</td>
</tr>
<tr>
<td>SD</td>
<td>12.3</td>
<td>12.9</td>
</tr>
<tr>
<td>Range</td>
<td>18-68</td>
<td>18-66</td>
</tr>
<tr>
<td>Sex, No. (%) of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (81.5)</td>
<td>15 (65.2)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (18.5)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>PASI at Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>22.6</td>
<td>27.5</td>
</tr>
<tr>
<td>SD</td>
<td>11.1</td>
<td>15.7</td>
</tr>
<tr>
<td>Range</td>
<td>6-47</td>
<td>8-70</td>
</tr>
<tr>
<td>Duration of disease, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>16.5</td>
<td>20.0</td>
</tr>
<tr>
<td>SD</td>
<td>9.9</td>
<td>10.4</td>
</tr>
<tr>
<td>Range</td>
<td>1-43</td>
<td>5-43</td>
</tr>
</tbody>
</table>

* PASI indicates Psoriasis Area Severity Index

### Table 3. Immunosuppressive Medication. Before Study Began*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Tacrolimus (FK506) (n=27)</th>
<th>Placebo (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other therapeutic products</td>
<td>4 (14.8)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Antipsoriatic topical agents</td>
<td>0</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Retinoids for treatment of psoriasis</td>
<td>3 (11.1)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Antimetabolites; folic acid analogues</td>
<td>3 (11.1)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>All other cytostatic agents</td>
<td>1 (3.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

* The number of medications was as follows: tacrolimus, 11; placebo, eight. The number (percentage) of patients in each treatment group was as follows: tacrolimus, six (22.2%); placebo, six (26.1%)
### Table 4. Patients responding to treatment*

<table>
<thead>
<tr>
<th>Week</th>
<th>Tacrolimus (FK506) (n=27)</th>
<th>Placebo (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No. (%) of patients</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>12 (63.2)</td>
</tr>
</tbody>
</table>

* Patients were defined as responding to treatment if the percentage change in the PASI from baseline after 3 weeks was 20% or greater, after 6 weeks 45% or greater, and after 9 weeks 70% or greater.

### Table 5. Primary reasons for withdrawal from the study

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Tacrolimus (n=27)</th>
<th>Placebo (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Event* or Adverse Event</td>
<td>2 (7.4)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>1 (3.7)</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>Lack of Efficacy and Withdrawn Consent</td>
<td>1 (3.7)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Lack of Efficacy and Adverse Event</td>
<td>1 (3.7)</td>
<td>0</td>
</tr>
<tr>
<td>Occurrence of Exclusion Criteria</td>
<td>1 (3.7)</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawn Consent</td>
<td>2 (7.4)</td>
<td>0</td>
</tr>
<tr>
<td>Full Remission</td>
<td>0</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8(29.6)</strong></td>
<td><strong>11(47.7)</strong></td>
</tr>
</tbody>
</table>

* One patient in the tacrolimus-treated group suffered an ischemic attack and circulatory collapse. These adverse events resolved and were not considered to be drug-related.
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Figure 1. Tacrolimus Dose Administration Throughout the Study Period

Results

Demographic and Baseline Characteristics

Fifty patients were enrolled into the study; 27 patients were randomized to the tacrolimus-treated group and 23 patients to the placebo-treated group. Comparison of baseline demographic data revealed no clinically significant differences between the two treatment groups (table 2). All the patients had a diagnosis of moderate to severe recalcitrant plaque-type psoriasis, and the mean PASI at baseline was 23 and 28 for the tacrolimus- and placebo-treated groups, respectively. Patients in both treatment groups had comparable relevant medical histories, as well as similar prior antipsoriasis therapy (table 3).

Figure 2. PASI: Percentage Relative to Baseline (Mean ± SEM)
**Dosing**

Figure 1 shows the tacrolimus dose administration throughout the study period.

**Efficacy**

Improvement with respect to the percentage change in the PASI relative to baseline was observed in both treatment groups at the end of week 3. By the end of week 9, the tacrolimus-treated group had a significantly greater median percentage change in the PASI compared with that of the placebo-treated group (tacrolimus, -83, placebo, -47, P<0.02, figure 2). A comparable number of patients in both treatment groups responded to therapy at the end of week 3; however, at weeks 6 and 9, more tacrolimus-treated patients responded to therapy than did placebo-treated patients (table 4).

Eight patients (29.6% [8/27]) in the tacrolimus-treated group and 11 patients (47.8% [11/23]) in the placebo-treated group were withdrawn from the study. Three weeks after the end of active treatment, 11 tacrolimus-treated patients (40.7% [11/27]) experienced a deterioration in the PASI while improvement was observed in four patients (14.8% [4/27]). In the placebo-treated group, two patients (8.7% [2/23]) had a deterioration in the PASI whereas improvement was noted in four patients (17.4% [4/23]).

**Safety**

**Causally Related Adverse Events**

Ten patients (37%) who received tacrolimus reported adverse events that were assessed by the investigator as being causally related to treatment compared with eight patients (34.8%) in the placebo-treated group. The most frequently reported adverse events are shown in table 6. All of the reported events were classified as mild or moderate in severity.

<table>
<thead>
<tr>
<th>Table 6. Most frequently reported causally related adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
</tr>
<tr>
<td><strong>Patients No. (%)</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Paresthesia</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>
Causally Related Adverse Events Leading to Withdrawal

Two patients who were randomized to tacrolimus treatment were withdrawn from the study because of adverse events that were assessed by the investigator as being causally related to treatment. One patient experienced diarrhoea, abdominal pain, paraesthesia or tremor, nausea, and palpitations. The second patient reported asthenia, erythema, hypertension, diarrhoea, pruritus, and paraesthesia. Whole-blood trough levels of tacrolimus measured in these two patients at the time of withdrawal were 14 and 6 ng/mL, respectively. The mean blood trough level of tacrolimus that was measured throughout the entire study period was 10 ng/mL.

One patient in the placebo-treated group was withdrawn from the study on account of pharyngitis, myasthenia, and paraesthesia.

Serious Adverse Events

A serious adverse event was classified according to the Food and Drug Administration definition. One patient in the tacrolimus-treated group experienced a transient ischaemic attack and concurrent circulatory collapse. These adverse events resolved and were not considered by the investigator to be drug-related.

Physical and Laboratory Parameters

A total of 24 tacrolimus-treated patients (88.9% [24/27]) and 18 patients (78.3% [18/23]) in the placebo-treated group had blood glucose values within the normal reference range throughout the study (reference range, 3 to 6 mmol/L). Five patients (21.7% [5/23]) in the placebo-treated group and three (11.1% [3/27]) in the tacrolimus-treated group had blood glucose values between 6 and 10 mmol/L (108 and 180 mg/dL). None of the patients in either treatment group required insulin therapy.

Although one patient experienced mild hypertension, no patients had clinically significant changes in blood pressure. All values were within the normal reference range between baseline and the end of active treatment at week 9. Haematological parameters and findings from urinalysis for all patients in both treatment groups were within the normal reference range. No major or sustained decrease in creatinine clearance was seen in either treatment group between baseline and the end of active treatment at week 9.

Discussion

No difference in efficacy was apparent between the two treatment groups after three weeks of therapy. Following an increase in dose in the majority of patients to 0.10 mg/kg per day at the end of weeks 3 and/or 6, the reduction in the PASI and the numbers of patients who responded to therapy were greater in the tacrolimus-treated group than in the placebo-treated group at the end of weeks 6 and 9. This may suggest that the minimal effective tacrolimus dose was 0.10 mg/kg per day.

The relapse rate after discontinuation of treatment was higher in the tacrolimus-treated group than in patients who were receiving placebo. The time to
relapse in cyclosporine-treated patients after the cessation of treatment ranges from a few weeks to several months. In the tacrolimus-treated group, the relapse rate steadily increases during the 3-week follow-up period, and it would therefore appear that patients who were receiving tacrolimus have the same time range of relapse as cyclosporine-treated patients.

The percentage reduction in the PASI that was observed at the end of week 3 was similar in the two treatment groups (-22 and -19 in the tacrolimus- and placebo-treated groups, respectively). Furthermore, there was little difference in the number of patients who responded to therapy between the two groups at this time point (table 4). This indicates that there was a considerable placebo effect that was not unusual for this type of study. Patients believe that the treatment is going to make them better, and consequently, they have a greater sense of psychological well-being that can have a positive effect on the disease. The use of emollients by the patients may also have contributed to the placebo effect as the removal of hyperkeratotic scales that contain proinflammatory mediators can lead to disease improvement. Another possibility is that, because of the cyclic nature of psoriasis, more patients in the placebo-treated group were already experiencing a natural improvement in their disease course.

The safety profile was similar between the two groups with the exception of mild-moderate diarrhoea that occurred only in the tacrolimus-treated patients. The predominance of diarrhoea in the tacrolimus-treated group may be related to the antibiotic properties associated with the macrolide structure of tacrolimus. Paraesthesia was also reported more often and by more patients in the tacrolimus-treated group. All causally related adverse events were either mild or moderate in severity in both treatment groups.

Renal dysfunction and hypertension are common problems in patients with psoriasis who are receiving short-term cyclosporine therapy. In this study, two tacrolimus-treated patients (7.4%) experienced mild or moderate renal dysfunction. One case of renal dysfunction, occurring in week 6, subsequently resolved without a change in the study medication. The other case of renal dysfunction was described as ‘ongoing’ at the end of the study. However, examination of the patient file found there to be no record of decreased creatinine clearance, and it is unclear whether this patient had renal dysfunction or if there was an error in the reporting of adverse events. Mild hypertension was reported by one patient (3.7%) in the tacrolimus-treated group, and again, it resolved without antihypertensive medication or dose reduction.

**Conclusion**

Tacrolimus appears to be efficacious in the treatment of severe recalcitrant plaque-type psoriasis compared with the efficacy of placebo. Most of the adverse events in the tacrolimus-treated group were causally related, mild to moderate in severity, and resolved without a reduction in dosage. In view of the pilot character of this study and the small number of patients, further studies that involve more patients are recommended to confirm these results.
Acknowledgements
This study was sponsored by Fujisawa Pharmaceutical Company Ltd, Osaka, Japan.
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CHAPTER 3

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3.5 Topical tacrolimus is not effective in chronic plaque psoriasis. A pilot study

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Abstract

Background: Cyclosporine for the treatment of psoriasis constitutes a new approach. Alternative systemic cyclosporine derivatives have been studied, to find an immunosuppressive drug with fewer adverse effects. Tacrolimus is one of these new immunosuppressive drugs. Systemically, it has been proven effective in treating psoriasis. A topical formulation of tacrolimus is attractive because it has fewer adverse effects and is useful for a large group of patients. We report for the first time on the efficacy of nonocclusive topical tacrolimus in the treatment of psoriasis.

Observations: After a washout phase of 2 weeks, patients were randomized to receive 0.005% calcipotriol ointment twice daily, placebo ointment once daily, or 0.3% tacrolimus ointment once daily. One psoriatic plaque was treated with a surface area of 40-200 cm². Efficacy was estimated using the local psoriasis severity index. The reduction in the local psoriasis severity index after 6 weeks was 62.5% in the calcipotriol group, 33.3% in the tacrolimus group, and 42.9% in the placebo group.

Conclusions: There was no statistically significant difference between the efficacy of tacrolimus and placebo ointment (P = 0.77). Calcipotriol ointment, applied twice daily, had a better effect than tacrolimus ointment and placebo ointment once daily.

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The introduction of systemic immunosuppressive therapy with cyclosporine for psoriasis forms a new approach in its treatment. Cyclosporine has also been found to be useful in other dermatological diseases, such as atopic dermatitis, lichen planus, and pyoderma gangrenosum. Alternative systemic cyclosporine derivatives have been studied to find an immunosuppressive drug with fewer adverse effects, i.e., hypertension and nephrotoxicity. Oxeclopsorine has been found to be effective in the treatment of psoriasis but was later found to have potential hepatotoxic effects (unpublished data, European Study Group, 1992), and thus was not further developed. Another promising drug is systemic tacrolimus. After initial uncontrolled studies, a placebo-controlled study was conducted by the European Study Group. When given systemically, tacrolimus was found to be effective in treating patients with psoriasis.

For dermatology, a topical formulation of these macrolactam-type cyclic immunosuppressive drugs is an interesting pharmaceutical option. The first studies with topical cyclosporine were performed in 1987. Topical cyclosporine was not effective, either in psoriasis or in allergic or atopic eczema. The ascomycine derivative, ASM 281-240 has also been used topically under occlusion in psoriasis, with promising results. However, a confirmatory study has not been published. Topical tacrolimus was studied in atopic eczema and contact allergy, where it has been successful. Topical tacrolimus also has been studied under occlusion on descaled psoriatic skin in micro plaques, and in this model topical tacrolimus showed efficacy.

We have studied the possible efficacy of topical tacrolimus in psoriasis in a 3-armed study for 6 weeks.

**Study design**

After a washout phase of 2 weeks, patients were randomized to receive 0.005% calcipotriol ointment twice daily, placebo ointment (ointment base free of tacrolimus) once daily, or 0.3% tacrolimus ointment once daily. The study was double-blinded except for the calcipotriol group for whom the investigator was not blinded because of the instruction to use the medication twice daily. Only 1 psoriatic plaque with a surface of 40-200 cm² was treated. Efficacy was estimated using a modified psoriasis area and severity index adjusted for 1 lesion, the local psoriasis severity index (LPSI). The minimum LPSI was 6.0 at entry.

**Results**

Seventy patients were studied: 23 in the calcipotriol group, 24 in the tacrolimus group, and 23 in the placebo group. At baseline, patients in the tacrolimus and calcipotriol groups had a median LPSI of 7.0, and the median LPSI in the placebo group was 8.0. After 6 weeks, the LPSI decreased by 33.3% in the tacrolimus group, 62.5% in the calcipotriol group, and 42.9% in the placebo group. There was no statistically significant difference (P = 0.77) between the efficacy of tacrolimus and placebo ointment. The difference between calcipotriol and tacrolimus ointment was statistically significant, as estimated by the 2-tailed Mann-Whitney test (P < 0.005).
Comment

This study shows that the tacrolimus ointment, when used once daily, was not better than a placebo ointment for the treatment of psoriatic plaques. The study also shows that calcipotriol ointment, used twice daily, had a better effect than tacrolimus ointment and placebo ointment used once daily. Because the effect of a placebo ointment used twice daily was not studied here, it is incorrect to conclude from this study that calcipotriol ointment is superior to placebo or tacrolimus ointment. It should be noted that this was a pilot study with relatively small numbers of patients and only indicates a direction.

Tacrolimus is a 822.05 d molecule that appears to be effective in atopic eczema but not in psoriasis when used as a topical drug. This result might be explained by assuming that the molecular weight prevents penetration into psoriatic skin. Systemic tacrolimus is effective in treating psoriasis. Because of a probable skin barrier defect, molecules with a molecular weight between 800 and 1200 d can penetrate the skin and thus are effective in treating atopic eczema. Furthermore, it is striking that all cyclic topical immunosuppressive drugs have a molecular weight greater than 800 d. Both corticosteroids (mean molecular weight around 450 d), and calcipotriol (molecular weight, 413 d), the 2 drugs that have been proven to be effective in psoriasis, have molecular weights less than 500 d. Until now the only exceptions to the 500-d barrier hypothesis are the studies with oxyclosporine (SDZ 281-240) by Rappersberger et al and the study with topical tacrolimus by Remitz et al, in which these macrolactams with a molecular weight slightly greater than 800 d were found to have an effect on psoriasis. The efficacy might be related to the occlusive effect of the Finn chambers used in these study. If a topical formulation could be designed that will enhance penetration in psoriatic skin by first disrupting the skin barrier function, macrolactam-type cyclic immunosuppressive drugs probably would be effective in a topical formulation. Another option is the development of cyclic immunosuppressant drugs with a lower molecular weight.
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