Discoid lupus erythematosus (DLE) is an autoimmune disorder with a variety of clinical presentations, localized in 80% of patients to the face, scalp, and ears, and in 20% of cases to the upper trunk and extremities. The most common age of onset is between 20 and 40 yr. The prevalence of cutaneous lupus varies from 14.6 to 68 per 100 000 people, with a female predominance between 20 and 40 yr. The prevalence of cutaneous lupus varies from 14.6 to 68 per 100 000 people, with a female predominance of 3:1 [1]. The diagnosis of cutaneous lupus erythematosus is based upon the presence of compatible clinical lesions, which on biopsy demonstrate a characteristic pathological picture [2]. In the absence of systemic disease, the focus of therapy is the skin. The goals of management in a patient with DLE are improvement of the patient’s appearance and prevention of deforming scars, well-defined, scaly plaques, which tended to heal with atrophy and telangiectasias [6]. Since cutaneous lesions may be the only manifestation of the disease, it is difficult to justify systemic agents because of their side-effects. Consequently, there is a need for steroid-free topical medications in the treatment of DLE.

Pimecrolimus (SDZ ASM 981) is the most recent member of a triad of calcineurin inhibitors: cyclosporin A, tacrolimus and pimecrolimus [7]. Whereas cyclosporin A and tacrolimus were originally developed for the prevention of graft organ rejection in transplant patients, pimecrolimus 1% cream was specifically developed for the treatment of inflammatory skin diseases [8]. Topical pimecrolimus has proved to be effective, safe and well tolerated in paediatric patients with atopic dermatitis [9–11].

We found studies on the efficacy of topical tacrolimus in diverse forms of cutaneous lupus, including DLE [12–14], but information about pimecrolimus is scarce. Therefore, in this open-label study, we decided to evaluate the efficacy and safety of pimecrolimus as monotherapy in patients with DLE.

Patients and methods

Study design and eligibility

In an open-label phase II clinical trial design, we evaluated the safety and efficacy of pimecrolimus 1% cream as monotherapy in patients with DLE. The patients were recruited from a dermatology out-patient centre. DLE was diagnosed if erythematous, well-defined, scaly plaques, which tended to heal with atrophy and scarring, were present together with histological epidermal atrophy and telangiectasias [6]. Since cutaneous lesions may be the only manifestation of the disease, it is difficult to justify systemic agents because of their side-effects. Consequently, there is a need for steroid-free topical medications in the treatment of DLE.
or alteration at the dermo-epidermal junction [6]. Patients included in the study were overall in good general health. A detailed history and physical examination, complete blood cell count, routine blood chemistry testing and urine analysis were performed in each patient before treatment. In order to rule out systemic lupus erythematosus (SLE), we used the American College of Rheumatology classification criteria [15]. Patients excluded from the study were those with other forms of cutaneous lupus and those who had a history of cardiovascular disease or coagulation disorder, an active malignancy, or previous exposure to pimecrolimus, tacrolimus or cyclosporin A. The study was approved by our Institutional Review and Ethics Committee and written informed consent was obtained from all patients before enrolment.

Patient evaluation

The efficacy and safety of the treatment was assessed at baseline and every 4 weeks during the 12 weeks of the study (from baseline to week 8 to evaluate efficacy and week 8 to week 12 to evaluate relapses). In order to measure the severity of DLE in each patient we used the clinical severity score. The method consisted of determination of the grades of erythema, infiltration and hyperkeratosis/scaling (0, normal; 1, slight; 2, moderate; 3, severe in each parameter) [16]. Total clinical score was determined by addition of the individual scores; the possible score ranged from 0 (normal) to 9 (maximum damage to the skin). Clinical assessment of individual patients was conducted by the same physician. The efficacy was also expressed as the patient’s overall assessment (as completely cleared, marked clearance, moderate improvement, slight improvement, no change or worse). The impact of DLE on the quality of life (QOL) was evaluated with the validated Spanish version of Skindex-29 [17]. In this instrument, the three impact dimension scores—emotional, functioning and symptoms—were used to derive a total index. Twenty-nine impact questions were used to construct the index. The possible QOL index score ranged from 0 (no effect on QOL) to 100 (maximum effect on QOL) [18]. The primary parameter for measuring the effects of pimecrolimus on DLE was the change in the clinical severity score from baseline.

Treatment protocol

After a washout period for previous DLE therapies (4 weeks for oral or parenteral steroids, chloroquine, hydroxychloroquine and thalidomide; 2 weeks for topical agents, including corticosteroids), patients were included in the screening phase. This was followed by 8 weeks of treatment with pimecrolimus 1% cream, twice daily on the affected areas. The amount of cream was restricted to a thin layer (1.5 g/10 cm²). There was no other systemic or topical treatment during the whole treatment period. Efficacy and safety were assessed at weeks 4 and 8. From week 8 to week 12, no treatment was allowed in order to evaluate the relapse rate.

Histological evaluation

Biopsy specimens (4 mm punch biopsies) of affected skin were obtained at baseline and from the same area at week 8 of treatment. The specimens were initially fixed in 10% neutral buffered formalin; paraffin-embedded tissues were sectioned at 5 µm thickness and stained with haematoxylin and eosin for histological examination. The analyses included the evaluation of surface hyperkeratosis, thinning of epidermis with vacuole degeneration of the basal cells, and dermal lymphoid cell infiltrate [6, 16]. The person examining the histological sections was unaware of the data from the patients.

Safety monitoring

Safety was assessed at the screening visit and every 4 weeks during the 12 weeks of the study by physical examination and routine laboratory evaluations, including the determination of liver transaminases, creatinine, urea, haemoglobin, haematocrit, white blood cell count (WBC), differential WBC, thrombocyte count and glucose. Adverse events were recorded and included those spontaneously reported by patients and those elicited by general questioning or by observation of the medical staff.

Statistical analysis

Data are presented as mean ± s.d. The paired t-test (Wilcoxon signed rank test for paired values) was used to evaluate the significance of differences in mean changes between baseline and subsequent visits for the calculated clinical severity score and QOL score. The analysis of laboratory variables was based on relative changes from baseline to subsequent visits by the use of paired t-tests (two-tailed). Differences were considered significant at P < 0.05.

Results

Patients

A total of 10 patients (one man and nine women) with a mean age of 34 ± 17 yr (range 5–56 yr) and a disease duration of 3.3 yr (range 1–8 yr) were studied. All patients included were considered to have moderate disease and four patients had failed to respond to at least two prior topic or systemic therapies in the past; all of them had used topical therapy, such as corticosteroids. All patients who were enrolled completed the 12-week study period. Demographic features and baseline disease characteristics of the study population are summarized in Table 1.

Efficacy

Clinical effectiveness was found in all patients. In the whole group, a significant mean reduction in the overall clinical severity score by 52% (from 6.1 ± 1.4 before treatment to 2.9 ± 1.5 after treatment; P = 0.005; baseline vs week 8) was observed. This resulted initially in a decrease in skin induration, erythema and squamation, and later in a decrease in plaque area (Fig. 1). The degree of improvement was heterogeneous; overall, three of the 10 patients achieved a decrease of at least 30% in the severity score; four patients showed a reduction of 50% or greater, and three patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr/sex)</th>
<th>Disease duration (months)</th>
<th>Topography</th>
<th>Previous therapies</th>
<th>Severity score (0–9)</th>
<th>Skindex-29 score (0–100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53/F</td>
<td>30</td>
<td>Face</td>
<td>2</td>
<td>7</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>50/F</td>
<td>42</td>
<td>Face</td>
<td>–</td>
<td>4</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>38/F</td>
<td>12</td>
<td>Face, scalp</td>
<td>2</td>
<td>5</td>
<td>32</td>
</tr>
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<td>4</td>
<td>43/F</td>
<td>96</td>
<td>Face, arms</td>
<td>–</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>18/F</td>
<td>60</td>
<td>Face</td>
<td>2</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>5/M</td>
<td>7</td>
<td>Face, scalp</td>
<td>–</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>42/F</td>
<td>84</td>
<td>Face</td>
<td>7</td>
<td>9</td>
<td>44</td>
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<tr>
<td>8</td>
<td>21/F</td>
<td>12</td>
<td>Face</td>
<td>–</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>56/F</td>
<td>48</td>
<td>Face, scalp</td>
<td>5</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>18/F</td>
<td>6</td>
<td>Arms</td>
<td>–</td>
<td>7</td>
<td>71</td>
</tr>
<tr>
<td>Mean</td>
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<td>39</td>
<td>Face 90%</td>
<td>1.2</td>
<td>6.1</td>
<td>42.8</td>
</tr>
<tr>
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<td>32</td>
<td>–</td>
<td>1.9</td>
<td>1.4</td>
<td>23.1</td>
</tr>
</tbody>
</table>
showed a reduction of more than 70%. The results from the Skindex-29 score between baseline and week 8 showed a mean improvement of 46%, from 42.8 ± 23.1 before to 23 ± 16.5 after treatment (significant; \( P = 0.008 \)). The distribution of the different domains indicated that the emotional score had the most significant impact on their disease, more frequently than for the symptoms and functioning domain scores, respectively. According to the patients’ overall assessment of the response to treatment, five of them qualified their disease as markedly cleared (50%), four obtained moderate clearance (40%) and one achieved a slight improvement (10%). There was a good agreement between disease severity and the QOL impact index.

All the skin biopsies showed the histological features of DLE with variable degrees of severity. After treatment, in all cases there was a decrease in hyperkeratosis, corneal plugs, and widening of the epidermis without vacuolar degeneration, and the infiltrate evaluated in a qualitative form also showed a decrease. Generally, the most significant improvement was the reduction in the density of the dermal lymphocytic infiltrate. Figure 2 shows the improvement in the clinical and histological parameters before and after treatment. Severity score, QOL index and histological changes over time for all patients are illustrated in Table 2.

**Safety**

None of the patients discontinued the treatment because of adverse events. The most frequent drug-related adverse effects were pruritus in four (40%) and erythema in two (20%) patients; these cutaneous complaints were reported within the firsts weeks of treatment and none required additional management. Haemoglobin levels, packed cell volume, erythrocyte count and WBC were unchanged in all patients. No clinically relevant or statistically significant changes were found in other laboratory variables. No patient relapsed during the 4-week follow-up period after stopping pimecrolimus.

**Discussion**

The main reason for developing new drugs as an alternative to topical steroids is to overcome side-effects, such as thinning of the skin and adrenal gland suppression, and recent studies have demonstrated that skin thinning is avoided with the use of pimecrolimus cream [19]. This pilot study demonstrates that pimecrolimus 1% cream as monotherapy was effective in the amelioration of the skin when compared with baseline, with a mean reduction of 52% in the severity score (\( P = 0.005 \)) and a mean improvement of 46% in QOL (\( P = 0.008 \)). All patients had moderate disease and nearly half of them had received previous topical or systemic therapies with variable responses. The onset of improvement began within the first month of drug application. The safety profile in this open trial is similar to those reported in previous atopic dermatitis clinical trials [20]. The main limitations of our study are the small number of patients included and the open rather than placebo-controlled design.

Zabawski [21] was the first to describe, in a single case report, a moderate improvement of DLE lesions under pimecrolimus ointment; however, he did not mention the schema employed, the duration of treatment or the method of assessing improvement. More recently, Kreuter et al. [22] reported on topical pimecrolimus in 11 patients with different forms of cutaneous lupus, including...
four patients with DLE, three with SLE, two with subacute cutaneous and two with lupus tumidum. The patients were treated with pimecrolimus twice daily, and the evening applications were followed by overnight occlusion with hydrocolloid dressings to increase the cutaneous uptake of the cream. Significant amelioration of the skin lesions was observed after therapy. Interestingly, the overall percentage of improvement was very similar (57% vs 52% in our study), but without using overnight occlusion. Moreover, we included an evaluation of QOL, which showed a mean improvement of 46%.

A few studies in DLE have included the analysis of QOL; this aims to measure objectively how the patient’s life is affected by the disease [23]. Skindex-29 is a generic and widely validated instrument to measure QOL in patients with skin diseases [17]. Therefore we employed the Spanish version of Skindex-29, which had demonstrated validity, reliability and sensitivity to change, which is an especially important issue for drug evaluation trials [18]. Systemic side-effects are absent with topical pimecrolimus, but topical side-effects include burning sensation, tingling, flushing and folliculitis at the application site [24]. In our study, however, minimal pruritus and erythema was observed in four and two patients, respectively, at the initiation of the treatment, but none required additional measures.

The activation of cutaneous T cells plays a crucial role in the pathogenesis of DLE, as demonstrated by Tebbe et al., who showed a predominance of CD4+ and CD8+ T lymphocytes and a high CD4/CD8 ratio in the immunophenotyping of the cellular components of the dermal infiltrate [25]. Increased expression of HLA-DR and adhesion molecules (ICAM-1 and LFA-1) on keratinocytes, endothelial cells, macrophages and lymphocytes indicates local immune-inflammatory activation [26].

Pimecrolimus belongs to the macrolactam immunosuppressive drugs, which inhibit T-cell activation. Intracellular calcium is increased in activated T cells and binds to calmodulin, which activates calcineurin, a calcium-activated phosphatase. Activated calcineurin dephosphorylates the transcription nuclear factor of activated T cells (NF-AT). Diphosphorylated NF-AT binds to its nuclear counterpart to form an active transcription factor that stimulates the production of cytokines [27]. Pimecrolimus inhibits the production and release of pro-inflammatory cytokines in T cells in vitro; this involves T-helper type-1 and type-2 cell cytokines, such as interleukin-2 (IL-2), interferon-γ, IL-4, IL-8 and IL-10, as well as tumour necrosis factor-α, thereby preventing the cascade of immune and inflammatory signals [28]. With regard to the efficacy of topical pimecrolimus vs tacrolimus, there is only one direct comparison in children with moderate atopic dermatitis; no statistically significant difference was found in the proportion of children clear or almost clear at 6 weeks [29].

Our data suggest that pimecrolimus 1% cream for DLE seems to be a safe and clinically effective option, especially for resistant DLE at sensitive sites such as the face, where the use of potent topical steroids carries a high risk of thinning of the skin and telangiectasia. However, the place of pimecrolimus in the treatment of cutaneous lupus will depend on its efficacy when compared with established topical treatments, such as corticosteroids. The present study had an open-label design and involved only a small number of patients and no control group, therefore double-blind, placebo controlled studies are needed in order to confirm our data.

### References