A Comparison of Oral Methylprednisolone Plus Azathioprine or Mycophenolate Mofetil for the Treatment of Pemphigus

Stefan Beissert, MD; Thomas Werfel, MD; Uta Frieling, MD; Markus Böhm, MD; Michael Sticherling, MD; Rudolf Stadler, MD; Detlev Zillikens, MD; Berthold Rzany, MD; Nicolas Hunzelmann, MD; Michael Meurer, MD; Harald Gollnick, MD; Thomas Ruzicka, MD; Hans Pillekamp, MD; Volker Junghans, MD; Thomas A. Luger, MD

Objective: To investigate the safety and efficacy of oral methylprednisolone combined with azathioprine sodium or mycophenolate mofetil for the treatment of pemphigus.

Design: A prospective, multicenter, randomized, non-blinded clinical trial to compare 2 parallel groups of patients with pemphigus (pemphigus vulgaris and pemphigus foliaceus) treated with oral methylprednisolone plus azathioprine or oral methylprednisolone plus mycophenolate mofetil.

Settings: Thirteen departments of dermatology in Germany.

Patients: We included patients with pemphigus vulgaris (n=33) or pemphigus foliaceus (n=7) evidenced by clinical lesions suggestive of pemphigus, intraepidermal blistering on histological analysis of skin biopsy specimens, intercellular deposition of IgG within the epidermis, and immunoblot analysis findings for antidesmoglein 3 and/or antidesmoglein 1 autoantibodies.

Main Outcome Measures: The cumulative total methylprednisolone doses and rate of remission. Secondary outcome measures were safety profiles and duration of remission.

Results: In 13 (72%) of 18 patients with pemphigus receiving oral methylprednisolone and azathioprine, complete remission was achieved after a mean±SD of 74±127 days compared with 20 (95%) of 21 patients receiving oral methylprednisolone and mycophenolate mofetil in whom complete remission occurred after a mean±SD of 91±113 days. The total median cumulative methylprednisolone dose used was 8916 mg (SD, ±29 844 mg) in the azathioprine group compared with 9334 mg (SD, ±13 280 mg) in the mycophenolate group. In 6 (33%) of 18 patients treated with azathioprine, grade 3 or 4 adverse effects were documented in contrast to 4 (19%) of 21 patients who received mycophenolate mofetil.

Conclusion: Mycophenolate mofetil and azathioprine demonstrate similar efficacy, corticosteroid-sparing effects, and safety profiles as adjuvants during treatment of pemphigus vulgaris and pemphigus foliaceus.

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Pemphigus is an acquired bullous autoimmune disorder of the skin and mucous membranes in which autoantibodies against keratinocyte antigens lead to a loss of cell-cell adhesion, resulting in erosions and blister formation. The autoantibodies are directed against epidermal cadherins, a family of calcium-dependent cell-cell adhesion molecules.1,2 According to clinical lesion appearance and autoantibody reactivity, pemphigus can be further classified into different subtypes, each with a characteristic intraepidermal loss of cellular attachments. By histological classification, the 2 major subtypes, pemphigus vulgaris and pemphigus foliaceus, are distinguished by the level of cleavage within the epidermis.3,4 Blister formation is more superficial in pemphigus foliaceus compared with pemphigus vulgaris. Pemphigus vulgaris accounts for about two thirds of all pemphigus cases and probably constitutes the most common bullous autoimmune disorder in the eastern countries of Eurasia. In the West, pemphigus vulgaris is less common.3

The major pemphigus vulgaris autoantigen is desmoglein 3 (Dsg3), a desmosomal cadherin.1,2 Anti-Dsg3 autoantibodies bind to the extracellular domain of the NH2 region of Dsg3, which is proposed to have a direct effect on the adhesive function of Dsg3. Accordingly, experimental injection of anti-Dsg3 autoantibodies into newborn mice induced epidermal blister formation similar to pemphigus vulgaris.6 The relevance of Dsg3 for the adherence of keratinocytes is demonstrated.
in mice with a spontaneous mutation in Dsg3 and in knockout animals with a disrupted Dsg3 gene induced by homologous recombination.7 Pemphigus vulgaris serum samples may also contain autoantibodies to desmocollins and Dsg1, the pemphigus foliaceus antigen.8-10 Dsg3 expression is restricted to the basal and immediate suprabasal layers of the epidermis, whereas Dsg1 is expressed in the superficial layers.11

There is no standard treatment of pemphigus fulfilling the criteria of evidence-based medicine, and there are few, if any, controlled studies on individual therapeutic strategies in pemphigus. Before the therapeutic use of corticosteroids, pemphigus was almost invariably a fatal disease with a mortality of more than 70%.12,13 Ever since, the high mortality could be reduced to less than 10%. Accordingly, even today, corticosteroids remain the mainstay treatment of pemphigus. However, the relatively high doses and long duration of treatment often required to control the disease lead to a variety of adverse effects, many of which are serious. Today, corticosteroids are usually given in combination with adjuvant immunosuppressant therapy to reduce the cumulative corticosteroid dose and adverse effects. Nevertheless, most patients who die of pemphigus today die of complications from the treatment. Therefore, the search for safe and effective treatment regimens is of particular practical interest. Among the different immunosuppressants, azathioprine sodium has been widely used since the late 1960s to control disease in patients with pemphigus (hereafter referred to as pemphigus patients).14 More recently, pemphigus was successfully treated with a combination therapy using mycophenolate mofetil.15-17 Therefore, we were interested in investigating and comparing the safety and efficacy of azathioprine vs mycophenolate mofetil, each in combination with oral methylprednisolone, for the treatment of pemphigus. We herein present the results of a national randomized multicenter study addressing this issue.

METHODS

STUDY PATIENTS

Thirteen dermatologic departments in Germany participated in this prospective, randomized investigation. The study protocol was approved by the ethics committee of the University of Münster, Münster, Germany, and written informed consent was obtained from each patient. Consecutive patients with pemphigus vulgaris or pemphigus foliaceus were eligible for entry if they met the following criteria: clinical lesions suggestive of pemphigus, intraepidermal blistering on histological analysis of skin biopsy specimens, intercellular deposition of IgG within the epidermis, and detection of anti-Dsg3 and/or anti-Dsg1 autoantibodies by immunoblot analysis. Exclusion criteria were treatment with oral or topical corticosteroids and other immunosuppressive drugs during the previous 4 weeks.

STUDY DESIGN

This multicenter, randomized, nonblinded clinical trial compared 2 parallel groups of patients with pemphigus vulgaris and pemphigus foliaceus treated with oral methylprednisolone in combination with azathioprine or mycophenolate mofetil. Because complete healing of the lesions, as defined by a complete reepithelialization of all previous lesions, was the first primary outcome measure, blinding was not regarded as necessary. The second primary outcome measure was the cumulative oral corticosteroid dose used until complete remission, allowing comparison of the corticosteroid-sparing effects of the 2 alternative immunosuppressants. Secondary outcome measures were duration of remission and safety profiles of the 2 treatment arms. Randomization was stratified according to the clinical center and performed centrally with the use of random numbers of 3 for each stratum. Patients were randomly assigned, irrespective of severity of disease, to receive 2 mg/kg of methylprednisolone once daily (Urbason; Aventis Pharma Deutschland GmbH, Bad Soden, Germany) with 2 mg/kg of azathioprine sodium (Imurek; GlaxoSmithKline GmbH & Co KG, Munich, Germany) or 2 mg/kg of methylprednisolone once daily with 1000 mg of mycophenolate mofetil (CellCept; Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) given twice daily (2 g/d). The initial dosage was maintained until blister formation ceased, crusts and erosions disappeared, and reepithelialization of previous lesions started. The corticosteroid dosage was subsequently reduced to 40 mg/d. Afterward, the corticosteroid dosage was sequentially reduced by 10 mg/d every 2 weeks until a dosage of 20 mg/d was reached, followed by reductions in 5-mg steps every 2 weeks until 10 mg/d was reached and in 2.5-mg steps every 2 weeks until discontinuation of treatment. After discontinuation of corticosteroid therapy, azathioprine or mycophenolate dosages were maintained at the initial dosage as monotherapy for an additional 12 weeks. Subsequently, azathioprine sodium was reduced by 0.5 mg/kg every 4 weeks to a dosage of 100 mg/d. Thereafter, the azathioprine sodium dosage was tapered in 25-mg steps every 4 weeks until discontinuation of treatment. Mycophenolate mofetil therapy was reduced in 500-mg/d steps every 4 weeks to 1000 mg/d. Afterward, the mycophenolate mofetil dosage was decreased in 250-mg steps every 4 weeks until discontinuation of treatment.

If new blisters developed 7 days after the initiation of therapy, the methylprednisolone dosage was increased by 1 mg/kg every 7 days until blister development ceased.

Relapse was defined as new blister formation during dosage reduction of methylprednisolone or immunosuppressants. If a relapse was noticed when the methylprednisolone dosage was at least 40 mg/d, the previous corticosteroid dosage that permitted control of the disease was given. If a relapse was noticed when the methylprednisolone dosage was less than 40 mg/d, including the phase of immunosuppressant monotherapy or its reduction, the corticosteroid dosage was increased to 40 mg/d and the initial immunosuppressant dosage was given.

BASELINE AND FOLLOW-UP EVALUATIONS

At baseline, each patient underwent physical examination followed by a complete blood cell count, liver function tests, blood pressure evaluation, fecal occult blood test, and urine analysis. In addition, abdominal ultrasonography, chest radiography, electrocardiography, quantitative computed tomography for determination of bone density, and ophthalmologic evaluation to measure inner eye pressure and to determine cataract status were performed. The extent and location of blisters and erosions were documented by a physician who was not otherwise involved in the study. At each follow-up visit (on days 7, 14, 30, 60, 90, 120, 150, 180, 270, 360, 540, and 720), the patient underwent physical examination, complete blood cell count, liver function tests, blood pressure evaluation, and stool and urine analysis, and the extent and location of blisters and erosions and the cumulative dose of
methylprednisolone that had been taken were noted. The date of any relapse was also noted. Any adverse effects of treatment were assessed, and their severity was graded as 1 for mild effects, 2 for moderate effects, 3 for severe effects, or 4 for life-threatening effects, according to the standard criteria of the World Health Organization.

STATISTICAL ANALYSIS

Cumulative corticosteroid dosages as the primary endpoint of the study were compared using the Wilcoxon rank sum test for independent observations. All other analyses presented herein are of a descriptive or a hypothesis-generating nature. Dichotomous and ordered categorical data were analyzed with the Fisher exact test and a corresponding exact permutation version of the Mantel-Haenszel test, respectively. Event-related data, such as the time to achieve a remission or the time to recurrence, were estimated according to the Kaplan-Meier method and eventually compared using the log-rank test. All event or censoring times were calculated from the time of randomization. All P values reported are 2 sided. Unless otherwise indicated, data are expressed as mean ± SD.

RESULTS

PATIENTS

Between October 1997 and October 2000, 47 patients with pemphigus underwent assessment for eligibility (Table 1). Three patients declined to provide written consent. Use of other medication effective against pemphigus (in 2 patients), diagnosis of another bullous autoimmune disorder (in 1 patient), and severe cardiac insufficiency (in 1 patient) were other reasons for exclusion. Of the remaining 40 patients, 33 had pemphigus vulgaris and 7 had pemphigus foliaceus. The 40 patients were randomly assigned to receive the methylprednisolone-azathioprine combination (AZA group; n = 18) or the methylprednisolone–mycophenolate mofetil combination (MMF group; n = 21) (Figure 1). After randomization, 1 patient withdrew written consent. Thirty-four patients (87%) were newly diagnosed as having pemphigus, whereas 5 (13%) had been previously treated for their disease. The mean duration of follow-up among the pemphigus patients was 438 days for the AZA group and 438 days for the MMF group.

DISEASE CONTROL AND RELAPSE

In all 18 pemphigus patients who were assigned to the AZA group (15 with pemphigus vulgaris and 3 with pemphigus foliaceus) and in all 21 pemphigus patients who were assigned to the MMF group (17 with pemphigus vulgaris and 4 with pemphigus foliaceus), disease progression was inhibited by day 30 ± 7 days. Complete healing of the lesions and remission was achieved in 13 (72%) of the 18 AZA group patients (Figure 2). Among the other 5 patients with incomplete healing (28%), 2 did not respond to treatment with the methylprednisolone-azathioprine combination, treatment had to be discontinued owing to severe adverse effects.
in 2 patients, and contact was lost with 1 patient. Complete healing of the lesions and disease remission was noted in 20 (95%) of the 21 MMF group patients. One patient from this group (5%) did not achieve remission (Figure 2). This patient was noncompliant and discontinued therapy prematurely.

Complete remission was achieved after a mean duration of 74 ± 127 days of treatment in the AZA group. In the MMF group, complete remission was noted after a mean of 91 ± 113 days (P = .05). The mean disease-free interval from the time when complete remission was achieved until recurrence of lesions was 258 ± 183 days for the AZA group and 123 ± 103 days for the MMF group (P > .05). The Kaplan-Meier graph in Figure 3 shows the rate without relapse in pemphigus patients over time, indicating that both adjuvants in the 2 treatment arms controlled disease equally well.

The data in Figure 4, depicting the duration until relapse of disease, was documented from the time of randomization until pemphigus patients developed a recurrence of disease during the reduction phase of treatment medication (P = .59).

One of the aims of this investigation was to determine whether the corticosteroid-sparing effect of either immunosuppressant would be superior. Therefore, the cumulative corticosteroid dose was calculated for each pemphigus patient after the beginning of treatment and through the documentation period for at least 720 days. The data in Table 2 show that pemphigus patients who were randomized to the AZA group received a median ± SD methylprednisolone dose of 8916 ± 29 844 mg. In the MMF group, the median ± SD methylprednisolone dose was 9334 ± 13 280 mg. In general, these numbers are similar and possibly reflect the comparable immunosuppressive potential of both drugs.

The results in Table 3 further demonstrate that 19 (54%) of 35 pemphigus patients received a cumulative methylprednisolone dose of 10 000 mg or less during the course of treatment. Nine (26%) of 35 patients received 10 001 to 20 000 mg of corticosteroids. The distribution of the pemphigus patients to the different corticosteroid dose groups (Table 3) was similar for the AZA and MMF adjuvant treatment groups. In summary, similar cumu-
lative corticosteroid concentrations were taken during therapy in both treatment arms.

**COMPLIANCE WITH TREATMENT AND ADVERSE EVENTS**

One patient showed no compliance, withdrew written consent, and discontinued treatment. Contact was lost with another patient.

Overall, 17 severe (grade 3) or life-threatening (grade 4) adverse effects were reported in 10 patients (Table 4). In 6 (33%) of 18 patients randomized to the AZA group, grade 3 or 4 adverse effects were documented, compared with 4 (19%) of 21 patients from the MMF group ($P > .05$). The results in Table 4 demonstrate that the adverse effects that are typically associated with the immunosuppressants used in this investigation, such as nausea ($P = .06$), vomiting ($P = .21$), elevated liver function test results ($P = .21$), and infections ($P = .86$), did not differ significantly between treatment arms. Together, the adverse effects and efficacy reported were not significantly different between the 2 treatment arms.

This randomized investigation demonstrates that pemphigus vulgaris and pemphigus foliaceus can be controlled equally well by methylprednisolone therapy in combination with adjuvant azathioprine or mycophenolate mofetil therapy. Both immunosuppressants had a similar effect on disease activity and a similar safety profile. The cumulative corticosteroid doses used to treat disease were comparable in both treatment arms, suggesting that the corticosteroid-sparing effect of one adjuvant was not superior to that of the other. Also, most of the adverse effects were equally distributed between the groups, with a slight but not statistically significant trend in favor of mycophenolate mofetil for inducing fewer grades 3 and 4 adverse events.

Corticosteroids are the mainstay of pemphigus therapy to this day because they constitute the only treatment that is able to rapidly inhibit new blister formation. In the past few years, several strategies for the use of corticosteroids to treat pemphigus have been advocated. The original recommendation by Lever and Schaumburg-Lever was to give patients a fixed daily dose of prednisolone (200-400 mg) over up to 8 weeks. After the healing of the lesions, the dosage should be reduced to a maintenance level of 15 mg/d. The treatment regimen proposed by Bystryn and Steinman took the variable course of pemphigus into account and recommended starting treatment with relatively low prednisolone dosages (20 mg/d). In patients with severe forms of the disease or in those who do not respond, the corticosteroid dosage is continuously increased until the disease activity is controlled. This higher dosage is maintained until most lesions are cleared and is then reduced every 2 weeks. Another approach is to treat pemphigus with corticosteroid megadose pulses (1 g/d). Although disease can be controlled by using these different treatment regimens, many patients develop severe complications of long-term use of corticosteroids; in 1 report, more pemphigus patients died of corticosteroid complications than of uncontrolled disease. Such developments sparked the hope that adjuvant therapy would reduce the total cumulative corticosteroid doses needed for treatment.

The immunosuppressive drugs established for adjuvant therapy of pemphigus are azathioprine and cyclophosphamide. Azathioprine has been used successfully for nearly 4 decades as an adjuvant in combination with corticosteroids. The active metabolite of azathioprine is mercaptopurine, which is intracellularly converted to 6-thioguanine acid. These metabolites inhibit lymphocyte proliferation and activation by interfering with several enzymes required for nucleotide replication, such as inositol monophosphate dehydrogenase, glutamine 5-phosphoribosylpyrophosphate amidotransferase, and adenylosuccinate synthetase. Azathioprine and its me-
monophosphate dehydrogenase, the essential enzyme for nolic acid exclusively and reversibly inhibits inositol tal models. Accordingly, fewer malignancies were documented. Two patients developed severe hypertension and 1 developed severe diarrhea. In another patient, corticosteroid-induced depression was diagnosed resolved after reduction of the methylprednisolone dosage.

One of the more recent adjuvant therapies for pemphigus is mycophenolate mofetil. This drug is approved worldwide for the prophylaxis of solid organ transplant rejections. After its approval in transplantation medicine, mycophenolate has been successfully used in patients with bullous pemphigoid or pemphigus vulgaris on a casuistical basis. Remission could be induced in pemphigus patients who did not respond to azathioprine therapy. Mycophenolate mofetil is the ester of mycophenolic acid, which is the active metabolite. Similar to azathioprine, mycophenolate mofetil inhibits the proliferation of lymphocytes by interfering with DNA replication. Mycophenolic acid exclusively and reversibly inhibits inositol monophosphate dehydrogenase, the essential enzyme for de novo guanine nucleotide synthesis. Additional specificity is obtained because mycophenolic acid appears to block isoforms of inositol monophosphate dehydrogenase expressed primarily in proliferating lymphocytes. In contrast to azathioprine, mycophenolate mofetil is nonmutagenic. Furthermore, mycophenolic acid has been shown to abrogate B-cell proliferation, which is important in autoantibody-mediated bullous diseases, and has a significant antitumoral effect in several experimental models. Accordingly, fewer malignancies were documented in transplant patients receiving mycophenolate for longer periods.

In patients with bullous autoimmune disease, mycophenolate mofetil was shown to be effective and well tolerated. These reports are consistent with our results, because the methylprednisolone–mycophenolate mofetil application was able to induce remissions in 90% of the pemphigus patients treated. However, the time needed to achieve disease control in 50% of the patients was about 30 days in the AZA group compared with about 75 days in the MMF group (Figure 2). Blockade of at least 3 different enzymatic pathways by azathioprine compared with the inhibition of primarily 1 pathway by mycophenolate mofetil may explain the slightly earlier remission after onset of therapy in the AZA group. Nevertheless, looking at the rate of remission after 200 days, mycophenolate mofetil treatment was shown to induce a 90% remission in these patients compared with 43% in those receiving azathioprine. This trend persisted after 600 days of treatment because 20% of the pemphigus patients were still not achieving effective control with azathioprine compared with 10% using mycophenolate mofetil. The recurrence rate during reduction of treatment was similar in both groups (Figure 3). After about 720 days, all patients had experienced a relapse, suggesting the benefit of prolonging the intervals during the reduction phase of treatment in future treatment regimens.

The profile of adverse effects of mycophenolate mofetil was similar to that of azathioprine. However, fewer grade 3 and no grade 4 events were noted (Table 3). In one patient from the MMF treatment group, arterial hypertension was documented, which required treatment. In another patient, a severe type 2 herpes simplex virus infection occurred that was successfully controlled by valacyclovir.

A key diagnostic feature in pemphigus is the anti-Dsg1/3 autoantibody titer, which correlates with disease activity. Mycophenolate mofetil treatment has been shown to reduce these titers to below detectable levels in selected pemphigus patients. These data agree with our results. Combination treatment with mycophenolate mofetil and methylprednisolone decreased the serum concentration of autoantibodies in all of the patients investigated, similar to the reduction of autoantibody titers in all patients receiving azathioprine and methylprednisolone. These findings were not significantly different between the 2 treatment arms (data not shown). A contraindication for receiving azathioprine is thiopurine methyltransferase deficiency, which appears in 0.3% of the population. However, we cannot completely rule out that the patients from the AZA group who developed adverse effects had reduced thiopurine methyltransferase activity. Mycophenolic acid plasma concentrations have been measured in transplantation patients who were treated with mycophenolate mofetil. Perhaps future evaluation of mycophenolic acid levels in pemphigus patients will help to determine these patients’ responsiveness to treatment. Because remission was induced in 90% of our pemphigus patients within 175 days, we believe that routine analysis of mycophenolic acid plasma concentrations is not necessary.

One important aspect of adjuvant therapy is to reduce the total cumulative corticosteroid dose required to achieve remission. To this end, a combination of cyclosporine and prednisolone therapy was shown to significantly reduce the total corticosteroid dose in pemphigus patients when compared with a historical control group. Comparable cumulative methylprednisolone doses were documented in our investigation in both therapy arms. These results suggest that, indeed, adjuvant therapy is able to reduce corticosteroid use. However, in this investigation, no pemphigus patient cohort was treated with corticosteroid-only immunosuppression.

Another important immunosuppressant for the treatment of pemphigus is cyclophosphamide. Cyclophosphamide is often used as a pulse treatment in combination with prednisolone, especially in eastern Eurasia. By inducing DNA cross-linkage, cyclophosphamide has a different mode of action compared with azathioprine and mycophenolate mofetil. Cyclophosphamide treatment is more effective but is related to a higher inci-
dence of adverse effects when compared with azathioprine or mycophenolate mofetil. Although azathioprine may typically induce severe cholestatic hepatitis and an increased long-term risk of malignancy, cyclophosphamide can cause hemorrhagic cystitis, bladder cancer, and infertility. The antitumoral effects of mycophenolate mofetil observed in experimental models and the reduced malignancy rate in transplantation patients receiving long-term treatment favor the use of this agent in pemphigus patients, especially because remission can be induced in a high percentage of the patients. To further study the clinical efficacy of different doses of mycophenolate mofetil in pemphigus vulgaris, an international clinical study was initiated in North America and Eurasia (Aspexa WX17796). Taking this together with our evidence, we find mycophenolate to be an effective and safe adjuvant for the treatment of pemphigus, and our findings expand the range of the therapeutic alternatives available for patient-tailored treatment.

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Author Affiliations: Departments of Dermatology, University of Münster, Münster (Dr Beissert, Freling, Böhm, and Luger), Medical School Hannover, Hannover (Dr Werfel), University of Kiel, Kiel (Dr Sticherling), University of Leipzig, Leipzig (Dr Sticherling), Municipal Hospital Minden, Minden (Dr Stadler), University of Würzburg, Würzburg (Dr Zillikens), University of Lübeck, Lübeck (Dr Zillikens), Faculty of Clinical Medicine Mannheim, University of Heidelberg, Mannheim (Dr Rzany), University of Cologne, Cologne (Dr Hunzelmann), University of Dresden, Dresden (Dr Meurer), University of Magdeburg, Magdeburg (Dr Gollnick), University of Düsseldorf, Düsseldorf (Dr Ruzicka), University of Ulm, Ulm (Dr Pillekamp), and University of Göttingen, Göttingen (Dr Junghans), Germany; and Division of Evidenced-Based Medicine, Department of Dermatology, Charité-Universitätsmedizin, Berlin, Germany (Dr Rzany).

Correspondence: Stefan Beissert, MD, Department of Dermatology, University of Münster, Von-Escharc-Strasse 58, D-48149 Münster, Germany.

Author Contributions: Drs Beissert and Luger initiated and designed the trial, had full access to all data for interpretation, and had final responsibility for the decision to submit for publication. Study concept and design: Beissert, Freling, Zillikens, and Luger. Acquisition of data: Beissert, Werfel, Freling, Böhm, Sticherling, Stadler, Zillikens, Rzany, Hunzelmann, Meurer, Gollnick, Ruzicka, Pillekamp, and Junghans. Analysis and interpretation of data: Beissert and Luger. Drafting of the manuscript: Beissert. Critical revision of the manuscript for important intellectual content: Beissert, Werfel, Freling, Böhm, Sticherling, Stadler, Zillikens, Rzany, Hunzelmann, Meurer, Gollnick, Ruzicka, Pillekamp, Junghans, and Luger. Statistical analysis: Beissert and Luger. Administrative, technical, and material support: Beissert, Werfel, Freling, Böhm, Sticherling, Stadler, Zillikens, Rzany, Hunzelmann, Meurer, Gollnick, Ruzicka, Pillekamp, Junghans, and Luger. Study supervision: Beissert and Luger.

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