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Evaluation of the Antipruritic Effects of Topical Pimecrolimus in Non-Atopic Prurigo Nodularis: Results of a Randomized, Hydrocortisone-Controlled, Double-Blind Phase II Trial

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Key Words
Chronic pruritus · Itch · Therapy · Transient receptor potential subtype vanilloid 1 · Substance P

Abstract
Background: In the treatment of atopic dermatitis, pimecrolimus has high antipruritic effects. ***Objective:*** To investigate the efficacy of 1% pimecrolimus cream in comparison to 1% hydrocortisone cream in non-atopic prurigo nodularis (PN). ***Methods:*** A randomized, controlled, double-blind study with intraindividual randomization was done in 30 patients (17 females, 13 males; mean age 58.5 years) with PN. ***Results:*** Pruritus intensity decreased significantly ($p < 0.001$) on both treated sides as early as after 10 days of treatment; scratch lesions improved ($p < 0.001$). Quality of life as assessed by the Dermatology Life Quality Index improved significantly. However, a significant advantage of pimecrolimus over hydrocortisone was not found. ***Conclusion:*** The results suggest that the non-steroid pimecrolimus is an effective alternative for PN treatment.

Introduction

Prurigo nodularis (PN) is a highly pruritic condition and is defined by the presence of numerous, symmetrically distributed, hyperkeratotic or erosive nodules [1, 2]. In about 50% of patients, the underlying cause is atopic predisposition or atopic dermatitis [2]. In the other half, systemic, neurologic or psychiatric diseases contribute to the development of itch. Due to a long-lasting, vicious itch-scratch cycle, nodules develop which are themselves itchy and contribute to maintaining the cycle [2, 3]. The therapy of pruritus, in particular pruriginous skin changes, is often quite difficult and, like chronic pain, has a major negative impact on the general condition of the patient, leading to physical and psychological fatigue [2, 3]. Therefore, there is a great need to find effective and tolerable antipruritic therapies.

The development of the topical calcineurin inhibitor pimecrolimus has led to considerable improvement in the treatment of atopic dermatitis [4], and there was a marked amelioration of pruritus as well [4–6]. There are also case reports on the antipruritic efficacy of pimecrolimus treatment in a series of itchy dermatoses (e.g. chronic irritative

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hand dermatitis, lichen sclerosus), including PN [6, 7]. Pimecrolimus and tacrolimus are assumed to have, like capsaicin, an antipruritic effect by virtue of their influence on sensory cutaneous neurons and the phosphorylation of transient receptor potential subtype vanilloid 1 (TRPV1) receptor [8, 9]. Therefore, pimecrolimus can be expected to have high antipruritic efficacy not only in the treatment of atopic dermatitis. Topical application of capsaicin is effective in PN; however, it needs to be applied six times daily in increasing concentrations [10]. Furthermore, it causes burning in erosive scratch lesions. In contrast, pimecrolimus needs to be applied only twice daily and thus appears highly promising. The aim of this randomized, controlled, double-blind trial was to compare the antipruritic efficacy of 1% pimecrolimus cream with that of 1% hydrocortisone cream in the treatment of PN.

Methods

Patients and Inclusion/Exclusion Criteria

We conducted a single-center, double-blind, within-participant right-left randomized controlled phase II trial comparing the two treated sides (target lesions) on the arms or legs with intraindividual randomization (right side: pimecrolimus; left side: hydrocortisone or the other way round). The trial was registered before study onset (EudraCT identifier: 2005-005638-10; ClinicalTrials.gov identifier: NCT00507832). The study cohort comprised 30 patients (36–69 years of age) with PN who were recruited at the Department of Dermatology, University Hospital of Münster. Eligible participants were all adults with PN on the arms or legs and pruritus intensity at the time of joining the study above a value of 3 on the visual analog scale (VAS) (0 = no pruritus, 10 = worst imaginable pruritus) on both target lesions. Further inclusion criteria were no current consumption or application of drugs against pruritus and signed informed consent. PN is defined by the presence of numerous, itchy and symmetrically distributed, red-brown nodules and has a typical appearance. Only patients with clinically typical PN were included. Previous to study inclusion, the diagnosis of PN was confirmed histologically. Atopic predisposition was ruled out by history and laboratory analysis.

Exclusion criteria were the presence of a predisposition for atopic dermatitis, bacterial superinfection of scratch lesions, pregnancy or breast feeding, no contraception in the case of women of child-bearing age, psychosomatic and psychiatric diseases, known active malignant diseases, diseases that might cause pruritus needing treatment, systemic immune suppression, use of tacrolimus, pimecrolimus, steroids or capsaicin in the 2 weeks immediately prior to the start of the study, intake of antihistamines, steroids, cyclosporine A and other immunosuppressive drugs, paroxetine and fluvoxamine, naltrexone, UV therapy until 2 weeks before start of the study, wound healing disturbances or disposition to keloid formation (in that case, no harvesting of neuropeptides). Patients taking medicines that favor bleeding or after-bleeding such as acetylsalicylic acid or phenprocoumon (in that case, possibly no harvesting of neuropeptides), having known allergies to pimecrolimus or hydrocortisone and those who had participated in previous studies within the past 4 weeks were also excluded.

Randomization

Patients were randomly assigned to receive either pimecrolimus at the target lesion on the left arm or leg and hydrocortisone at the target lesion on the right arm or leg twice daily, or the other way round. For allocation of the participants, a list of random numbers was used for simple randomization between the two treatment groups. The investigator assigned each patient the lowest available number on the randomization list. The pimecrolimus and hydrocortisone formulations were blinded in the pharmacy of the University Hospital of Münster by filling them in identical tins identified as A or B, respectively. They were also identical in labeling, schedule of administration, appearance and taste. Patients received detailed advice and written information on how and on which side to use cream A and B. Patients, physicians and outcome assessors were kept blinded to the allocation.

Visit Plan, Intervention and Outcomes

There were a total of 5 study visits (V1: day 1 and start of therapy; V2: day 11 ± 3 days; V3: day 29 ± 3 days; V4: day 57 ± 3 days and end of therapy; V5: day 85 ± 3 days follow-up). Patients received both creams at their first visit. Creams were to be applied according to precise instructions twice daily within the following 57 consecutive days. Each arm/leg was treated with one of the creams. The patients treated the full length of the affected area, not only single lesions. At V1, patients were given a pruritus diary booklet. Daily pruritus intensity on the VAS ranging from 0 to 10, mean as well as maximal, for each side of the body was documented in this diary. At V2–V5, relative pruritus change in comparison to treatment beginning was rated by the patients (0% = no improvement, 100% = complete pruritus stop). In addition, at each visit, the patient marked the current pruritus intensity on the VAS. During V1–V5, the extent of scratch lesions (erythema, papules, nodules, excoriations and crust formation) was assessed using a prurigo score (PRUNOSI). The PRUNOSI was developed for this study in an expert panel of 5 experts (4 dermatologist, 1 psychologist). In brief, typical skin lesions of PN patients were defined (see above). Each item was assessed separately with a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The five values for each side were then summed up to a total value.

The sample size calculation was based on the primary efficacy endpoint (see below): change in the mean itch VAS between day 1 and day 11. Assumptions were as follows: $\alpha = 2.5\%$ (one-sided testing), power = 75%, assumed mean difference in the VAS between treatments = 1 cm with assumed standard deviation of the differences = 2 cm.

Biomarker

One secondary parameter of efficacy was the change from baseline of skin neuropeptides, which are increased in PN skin [11]. Hyperplasia of nerves in PN is associated with an increase of sensory neuropeptides, which is speculated to be related to pruritus [11]. Before and after 8 weeks of therapy, perilesional suction blisters were harvested bilaterally (in each case five blisters about 4 mm in diameter, arising from suction pressure, were harvested) in order to determine neuropeptide levels. Blister fluid (serum) was drained and deep-frozen. Levels of neuropeptide substance P (SP) and calcitonin gene-related peptide (CGRP) were investigat-

ed in the serum samples. For this, commercially available enzyme immunoassay kits (ACE competitive EIA for SP, Cayman Chemicals, USA, and CGRP, SPI Bio, France) were used. Measurements were carried out with a BioTek EL808 microplate reader. Results are presented as mean values in pg/ml of the serum plus standard deviation.

Statistics

All data were entered as Excel data by colleagues trained in data input and were analyzed with SPSS 18.0. Both intention-to-treat (ITT) and per-protocol (PP) analyses were carried out. All patients who had been randomized and had received at least one application of the study medication with a baseline and at least one post baseline evaluation of efficacy were included in the ITT analysis (n = 28). The data reported here refer to ITT analysis. Missing values during the treatment period V2–V4 were replaced by the corresponding immediately preceding values (last observation carried forward). Patients available for ITT analysis who completed the planned duration of the study, were compliant to the study procedures, had a valid final efficacy evaluation and did not violate the protocol in any way liable to influence efficacy outcome were valid for PP evaluation (n = 23).

The primary criterion was change in pruritus intensity on the VAS within the first 10 days of treatment, and the secondary criterion was test of superiority of pimecrolimus 1% cream over hydrocortisone cream 1% in terms of the following characteristics: change from baseline in PRUNOSI and neuropeptide SP and CGRP. Differences between the efficacy of the two creams were subjected to one-sided tests of significance with a significance level of $p = 0.025$. Analysis of variance was performed for the comparison of the treatments over time. T tests for dependent samples were carried out when comparing the preparations at one single time point (e.g. in case of percentual scores on change). We did not conduct baseline comparisons, for instance with regard to severity of PN, because of the within-subject design and because we included only patients with symmetrical distribution of PN.

The study was carried out according to ICH-GCP and in accordance with data protection regulations and with the permission of the ethics committee of the Medical Council Westphalia-Lippe and the Westphalian Wilhelms University Münster (permission No: 2006-279-f-A and BfArM No: 4032257). Informed signed consent was obtained from all patients.

Results

Demographics and Compliance

Patients were recruited between April 2007 and June 2009. The cohort consisted of 17 women (56.7%) and 13 men (43.3%), with age ranging from 36 to 69 years (mean 58.5 years). Duration of pruritus was between 10 months and 20 years (mean 74.8 ± 63.7 months). Patients had undergone between 1 and 11 therapies prior to inclusion in the study (mean 4.0 ± 2.4 therapies).

Out of the 30 patients, 12 (40%) were randomized to receive pimecrolimus on the right and hydrocortisone on the left body side, and 18 patients the other way round. A total of 5 patients dropped out of the study on grounds, for example, of disease progression (worsening of PN and/or itch; fig. 1). Two of these patients already dropped out before V2 was conducted (worsening of PN and/or itch, n = 1; no reason provided, n = 1). 28 patients continued and could be included in the ITT analyses. After V2, 1 patient discontinued because of contact allergy towards wound dressing after the suction blister procedure. After V3, 2 patients discontinued the study because of progression. In 22 patients (73.3%), treatment was carried out on their arms and in 8 (26.7%) patients on their legs; 23 patients (76.7%) reported using the cream regularly and 6 (21.4%) reported having failed to do so for different reasons (e.g. forgot to apply the cream); 1 patient did not answer the question of having regularly used the cream. Given that this concerned only single applications (once n = 4, twice n = 1, trice n = 1), we did not exclude these patients from the analysis.

In 4 patients, five adverse events were documented (tooth root inflammation, suspicion of allergy to plaster and chills, inflammation in the region of the suction blister, progression, bronchitis). None of these was a serious adverse event. In 1 case only (progression) was an association with the study medication suspected. Two of the adverse events led to dropouts before V3 (contact allergy) and V4 (progression), respectively.

VAS at Visits

From V1 to V2, there was a mean reduction in pruritus intensity of 2.7 ± 3.0 VAS units on the side treated with pimecrolimus and of 2.8 ± 3.2 on the hydrocortisone-treated side. Looking at the side treated with pimecrolimus, there was a highly significant improvement from V1 to V2 (VAS V1: 7.1 ± 2.2; V2: 4.4 ± 2.8; n = 28; $p < 0.001$) and also from V1 to V3, V4, and V5 ($p < 0.001$). The side treated with hydrocortisone also showed highly significant amelioration of pruritus from V1 to V2 (VAS V1: 7.3 ± 2.2; V2: 4.5 ± 2.8; $p < 0.001$) and from V1 to V3–V5 ($p < 0.001$). In the confirmatory analysis, there was, however, no significant difference between the two treatments ($p = 0.394$).

VAS Diary

Depending on the day, between 13 and 28 patients noted pruritus intensity in their VAS diaries. With time, there was a reduction in the number of patients who documented intensity of pruritus. Mean maximal intensity on the pimecrolimus-treated side ranged between 3.6 (day 23) and 5.4 (day 2); on the hydrocortisone-treated side, it was between 3.7 (day 52) and 5.4 (day 3). Comparison of mean values over the whole study period as

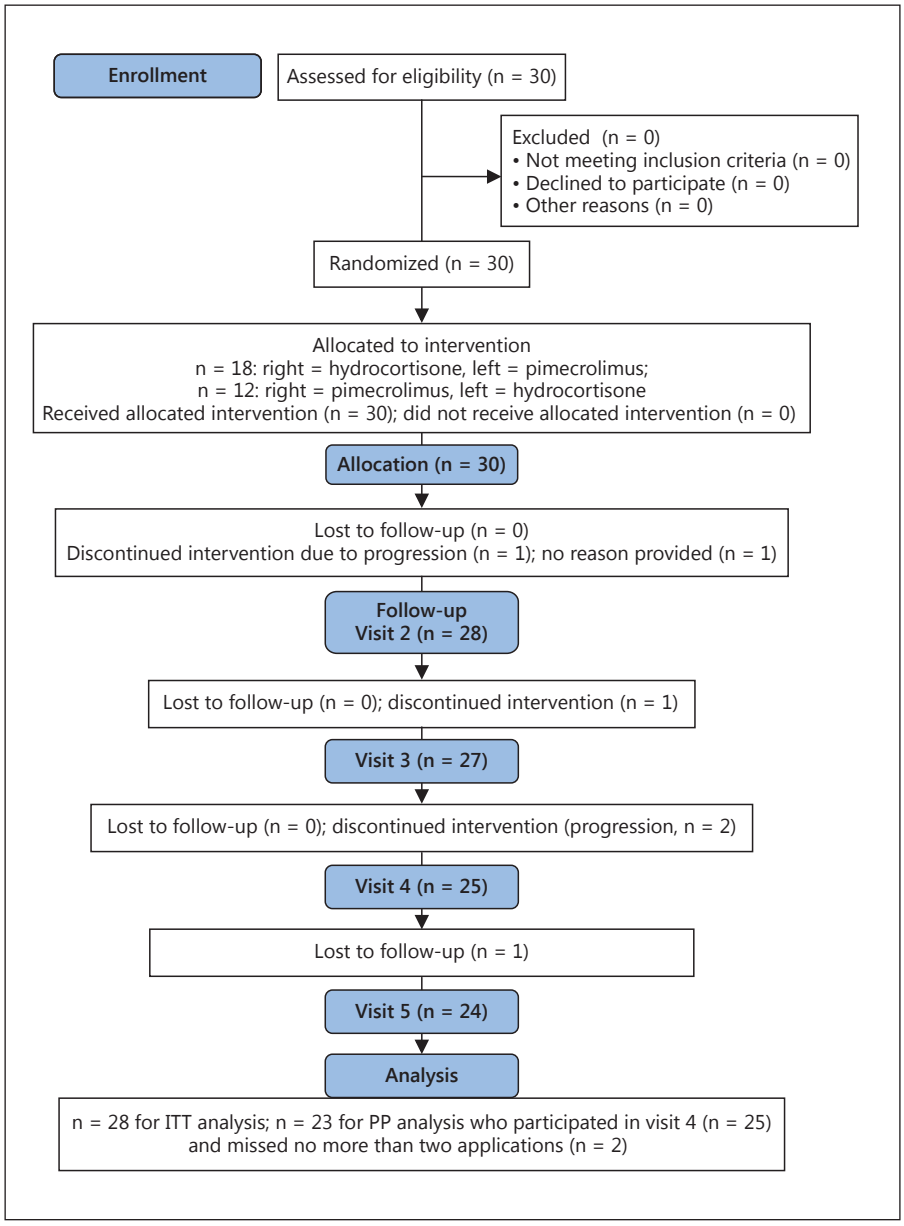

Fig. 1. Flow diagram with the patients and dropouts. 'Progression' refers to worsening of PN and/or itch.

well as from day 1 to day 11 (V1 to V2) showed no systematic differences between the two preparations.

Percentual Itch Reduction

Evaluation of the percentual scores showed a mean pruritus reduction of 35.9, 37.0 and 35.7% at V2, V3 and V4, respectively, on the pimecrolimus-treated side; on the hydrocortisone-treated side, there was a mean improvement of 39.1, 39.2 and 36.7%. There was no significant difference between the two creams regarding this parameter ($p > 0.1$).

Quality of Life

Disease-specific quality of life in the past 7 days as assessed with the Dermatology Life Quality Index (DLQI) (possible range 0–30 [11]) showed improvement from V1 to V2–V5 (fig. 2). DLQI decreased from 11.5 points (large impact on quality of life) to 8.0–9.6 points (V2–V4; moderate impact on quality of life). This effect was significant for V2 and V3 ($p < 0.05$). The DLQI cannot be compared between the two preparations because quality of life cannot be evaluated separately for the two differently treated sides.

Table 1. Results of PRUNOSI and its single parameters at V1 and V4

Substance/ visit	Total PRUNOSI	p	Papule	p	Nodule	p	Erythema	p	Excoriation	p	Crust	p
Pimecrolimus												
V1	4.1±1.6	0.013	0.4±0.72	0.083	1.13±0.73	0.782	0.37±0.56	0.102	1.13±0.63	0.020	1.07±0.52	0.035
V4	3.3±2.1		0.12±0.32		1.12±0.83		0.2±0.41		0.84±0.47		0.8±0.58	
Hydrocortisone												
V1	4.4±1.6	<0.001	0.4±0.77	0.157	1.27±0.78	0.153	0.4±0.56	0.014	1.13±0.63	0.008	1.17±0.65	0.001
V4	3.0±1.9		0.2±0.5		1.0±0.71		0.16±0.37		0.72±0.46		0.64±0.49	

Typical skin lesions of PN (erythema, papules, nodules, excoriations and crust formation) were assessed and rated separately on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The five values for each side were then summed up to a total value (PRUNOSI). After 8 weeks, a significant reduction was observed in excoriations, crusts and erythema (the latter only in hydrocortisone-treated lesions). There was no statistically significant difference between the two substances (ITT analysis).

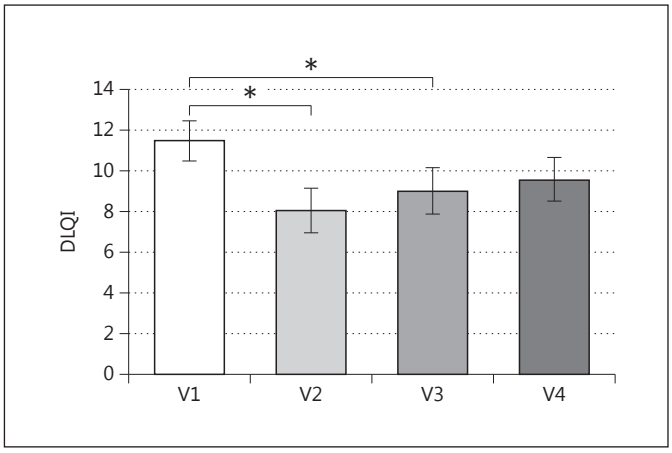

Fig. 2. Quality of life improved significantly within the first 30 days. DLQI decreased from 11.5 points (very large impact on quality of life) to 8.0–9.6 (V2–V4; moderate impact). Mean ± SEM; * $p < 0.05$.

Prurigo Lesions

Scratch symptoms as assessed with the prurigo score (PRUNOSI) were reduced by both substances from V1 to V2–V4 ($p < 0.025$) (table 1). On the pimecrolimus-treated side, the average PRUNOSI at V1 was 4.1 ± 1.6 and 3.4 ± 2.2, 3.3 ± 1.9 and 3.3 ± 2.1 at V2, V3 and V4, respectively. On the hydrocortisone-treated side, the mean PRUNOSI values were 4.4 ± 1.6 at V1 and 3.3 ± 1.8, 3.3 ± 1.9 and 3.0 ± 1.9 at the following visits V2–V4. For the period V2–V4, the time effect was highly significant ($p < 0.01$). No significant superiority of pimecrolimus over hydrocortisone in terms of reduction of scratch lesions was found.

Neuropeptides

In 15 patients, perilesional suction blisters were harvested at V1 and V4, in 5 patients only once. In 8 patients, no suction blisters were performed (e.g. because of therapy discontinuation, intake of acetylsalicylic acid or patient wish). Comparing the serum CGRP concentration before and after therapy with pimecrolimus, there was a reduction of on average 5.1 pg/ml (10.2%) in the CGRP concentration in the blister fluid (V1, mean 49.93 ± 22.0 pg/ml; V4, 44.83 ± 18.45 pg/ml; $p > 0.05$). There were almost no differences in the CGRP concentrations in the serum between before and after therapy with hydrocortisone (V1, 41.52 ± 29.11 pg/ml; V4, 41.45 ± 25.15 pg/ml; $p > 0.05$). Comparing the serum SP concentration before and after therapy, there was an increase of on average 2.08 pg/ml (14% increase; pimecrolimus; V1, mean 14.08 ± 5.9 pg/ml; V4, 16.16 ± 5.31 pg/ml; $p > 0.05$) and 0.77 pg/ml (6.1% increase; hydrocortisone; V1, mean 12.62 ± 2.87 pg/ml; V4, 13.39 ± 2.94 pg/ml; $p > 0.05$). All changes for CGRP and SP were not significant; we did not observe a significant down-regulation of neuropeptides (fig. 3).

Discussion

In this study we have been able to show that both pimecrolimus and hydrocortisone have significant antipruritic effects in PN ($p < 0.001$). This effect could be measured as early as 10 days after the start of therapy and contributed to clinical improvement of prurigo nodules (measured with PRUNOSI). The study design was intraindividual, i.e. one substance was applied on either side. Parallel to an amelioration of pruritus on both sides, there was, as a whole, sig-

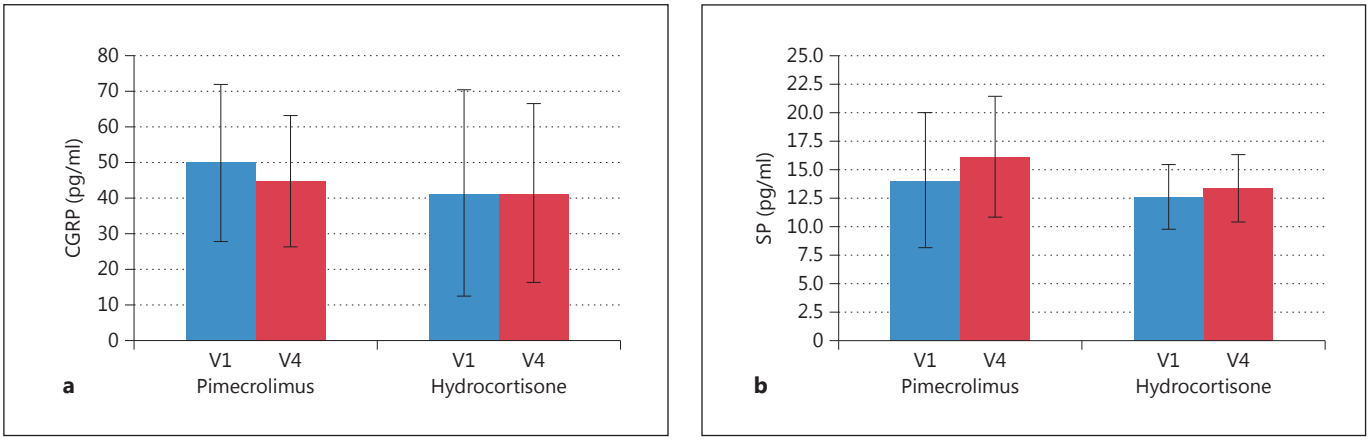

Fig. 3. CGRP (**a**) and SP (**b**) concentrations in the suction blister fluid at V1 and V4 (after 57 days of treatment). There were only slight, non-significant changes in the neuropeptide content of the skin after therapy with pimecrolimus or hydrocortisone.

nificant improvement ($p < 0.05$) in the dermatological quality of life (measured with the DLQI [12]).

These results are of interest since they suggest a non-steroid-based alternative treatment option of PN. Pimecrolimus was demonstrated to be effective in patients with an atopic background [4]. In this study, we demonstrated that pimecrolimus is even effective in PN patients with a non-atopic background. PN continues to be difficult to treat, and a satisfactory unitary concept is currently unavailable [2]. Besides topical steroids and antihistamines, gabapentin and cyclosporine A [13], thalidomide [14], hypnosis and acupuncture [15], capsaicin and vitamin D3 preparations [16] have been recommended for the treatment of PN. The efficacy of topical steroids in PN has been established in several studies. A recent study has demonstrated the antipruritic efficacy of betamethasone valerate 0.1% [17]. Previous studies have reported on the efficacy of hydrocortisone in PN [18, 19] so that this substance could be used as a comparator in this study. One important finding of this study is that topical application of pimecrolimus seems to be equally effective in non-atopic PN. Pimecrolimus represents an effective and non-atrophogenic, immunosuppressive drug which can be used for a longer time period than topical steroids. Long-term use of pimecrolimus over a period of more than 8 weeks appeared to be as effective as hydrocortisone in reducing pruritus.

PN is difficult to treat because of the variable underlying diseases and the highly resistant nodules. Treatment of PN usually requires a combination therapy of topical and systemic drugs over a long period of time [13]. Based on some studies and experience, the current guideline suggested gabapentin, cyclosporine, and others for certain underlying diseases in PN [13]. For example, in underlying kidney disease or neuropathy gabapentin is effective. Cyclosporine has a considerable antipruritic effect in atopic forms of PN. In addition, in most patients a topical therapy is necessary. Based on the results of the present study, the adjuvant use of pimecrolimus may be taken into consideration as part of a multimodal therapy concept. Compared to topical steroids, pimecrolimus might be less or equally potent, but has a less atrophogenic potency and can be used for a longer period than steroids.

Pimecrolimus is known for its immunosuppressive and antipruritic effects in atopic dermatitis [4]. In the present study, the antipruritic effect of this medication in non-atopic PN is shown for the first time. For the present, the mechanism of antipruritic action can only be speculated upon. Investigation of the suction blisters showed no significant changes in neuropeptide levels between pimecrolimus and hydrocortisone-treated skin. PN shows marked morphological remodeling processes in the affected skin [20, 21]. For instance, changes in epidermis and nerve fiber anatomy as well as connective tissue cells have been reported [21, 22]. In addition, there is variable dermal inflammatory infiltrate, with T lymphocytes and eosinophilic granulocytes predominating [22]. Cytokines from these cells such as interleukin-2, -6, -8 or -31 lead to maintenance of pruritus [23]. By direct receptor activation of the sensory neurons, they can act as pruritogenic agents [23]. Neuroreceptors in the skin are sensitized by continuous stimulation with ligands or other inflammatory mediators (such as bradykinin and pros-

taglandin), which results in the so-called peripheral sensitization, with alloknesis (pruritus caused by non-pruritogenic stimuli) and light pruritus triggering by low concentrations of ligands. Eosinophilic granulocytes promote this process by releasing neurotropins, which activate nerves by directly binding to them [23]. The anti-inflammatory effect of hydrocortisone is probably linked to its antipruritic efficacy, which in turn promotes healing of prurigo nodules. Pimecrolimus had equally good antipruritic effects in this study. Here too, it can be speculated that pimecrolimus exerts its antipruritic effect by its intervention in the inflammatory cascade. By inhibition of the phosphatase calcineurin, dephosphorylation and activation of the transcription factor NF-AT (nuclear factor of activated T cells) is prevented, and synthesis of T cell-activated cytokines such as interleukin-2 is blocked [4, 24]. It has been suggested that topical calcineurin inhibitors have a direct effect on heat receptors and the capsaicin receptor TRPV1 [8, 9, 25]. Activation of TRPV1 leads to neurogenic inflammation, which, in turn, can cause burning pain. It has been suggested that this is the underlying mechanism of burning sensation reported by some patients treated with pimecrolimus [25, 26].

Should long-term therapy with pimecrolimus indeed lead to inhibition of TRVP1, one could then expect a significant reduction in neuropeptide levels in the tissue, which, however, was not observed in our study. A recent study of the gene expression profiles of a topical steroid (betamethasone) and pimecrolimus demonstrated differences between the two substances, in particular in relation to epidermal genes [27]. In contrast to the steroid, pimecrolimus led to full restoration of the skin barrier [27], which is certainly beneficial and might be an explanation for the healing of PN lesions.

On the basis of the data of this study with intraindividual design, it has not been possible to confirm the hypothesis that pimecrolimus is better than hydrocortisone in reducing pruritus. Though pruritus was reduced to a high extend on the VAS (drop of 2.7 ± 3.0 and 2.8 ± 3.2 VAS units, respectively), a careful consideration of the VAS values for the treated sides shows that there is only a small difference in pruritus reduction between the substances. How far patients are able to differentially describe severity of symptoms on two body sides is a matter of speculation. One further limitation of this study is that daily application of creams on the sides they were intended for could not be monitored; only the total amount of creams used was monitored. It must also be kept in mind that the VAS as used in the diaries is a very difficult tool to employ in pruritus assessment since it can be influenced by many exogenous and endogenous factors [28, 29]. New tools are urgently needed to measure pruritus in a valid way. Furthermore, we used the PRUNOSI in this study. Interestingly, it demonstrated that the PRUNOSI parameter crusts and excoriations decreased significantly with both substances. As reduction in itch and scratching allows healing of excoriations/crusts, and as papules and nodules need months to heal, this result is not unexpected. However, this instrument has not been validated yet. Accordingly, the results have to be interpreted with caution.

A study design using comparison of sides might possibly lead to a leveling of reports on the subjective pruritus intensity. Therefore, a comparison in two parallel patient groups might be more suitable, which was not possible given the design of this study. The ability of both substances to cause a highly significant reduction in pruritus, however, does suggest that they exert a specific effect.

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Disclosure Statement

M. Bräutigam is an employee of Novartis.

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