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ORIGINAL CONTRIBUTION

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# Efficacy of a skin care cream with TRPV1 inhibitor 4-t-butylcyclohexanol in the topical therapy of perioral dermatitis

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## Abstract

**Background:** Perioral dermatitis is a clinically distinctive reaction pattern of facial dermatitis, including redness, dryness, burning, pruritus and skin tightness. A gold standard treatment remains unclear.

**Objectives:** Our study evaluates the clinical value of a skin care cream with the transient receptor potential vanilloid type 1 inhibitor 4-t-butylcyclohexanol in POD patients over 8 weeks.

**Methods:** This open, unblinded 8-week clinical trial included 48 patients. A skin care cream containing 4-t-butylcyclohexanol was applied over a period of 8 weeks. Standardized questionnaires were used at baseline, 4 and 8 weeks, for history documentation, objective and subjective severity scores, and quality of life assessments. Six different skin physiology parameters were assessed at all timepoints.

**Results:** The perioral dermatitis severity score decreased significantly during the treatment period. This was mirrored by significantly lower patients' subjective numerical rating score and an improved quality of life score. Transepidermal water loss, stratum corneum hydration and skin erythema improved significantly during the treatment period.

**Conclusion:** This transient receptor potential vanilloid type 1 inhibitor-based skin care cream improved subjective and objective parameters of perioral dermatitis. Decreased transepidermal water loss values and increased stratum corneum hydration demonstrate a restored skin barrier function. Consequently, the topical inhibition of these receptors is a promising management option for POD.

KEYWORDS
perioral dermatitis, POD severity index, topical therapy, transepidermal water loss

## 1 | INTRODUCTION

Perioral dermatitis (POD) first described in 1964 by Mihan and Ayres is a clinically characteristic skin reaction pattern typically affecting the perioral area and the perinasal/periocular areas with erythema and papules.[1] Patients are mostly women aged between 15 and 45 years and complain about skin tightness and burning sensation more than about pruritus. POD runs a chronic course due to treatment failure or noncompliance, leading to a substantial psychological burden.[2]

Hypotheses raised to explain the pathogenesis of POD suggest that this condition is the result of a vicious circle consisting of excessive skin care, disruption of the barrier function, and an increase in transepidermal water loss (TEWL), which leads to subjective skin dryness, resulting in the patient overusing moisturizers. Additionally, many patients are known to be atopic. The intermittent use of potent topical steroids is an established risk factor for POD.[3,4]

POD treatment is mainly based on clinical experience, and there is one published guideline on POD management.[5] Zero therapy is an established approach, but the low patient compliance is further reduced by an initial exacerbation. Two randomized, double-blinded, placebo-controlled clinical trials with pimecrolimus cream have been published.[6,7] Several other, less well-controlled studies have evaluated topical metronidazole and erythromycin, as well as some systemic antibiotics.[5] The clinical value of twice daily application of a drug-free cosmetic fluid has also been reported.[8]

As none of the known treatment options seems optimal, and the role of inhibiting TRPV1 receptors in treating sensitive skin is already established,[9] we decided to evaluate a skin care cream with the TRPV1-inhibitor 4-t-butylcyclohexanol to improve the objective parameters and subjective symptoms of POD.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

Our trial was a single-center, open-label, unblinded, 8-week study. Inclusion criteria for our study were adult patients presenting with a clinical diagnosis of POD. Exclusion criteria were planned medical treatment with topical metronidazole, erythromycin, pimecrolimus or oral tetracycline. There was no screening or washout phase.

A 50 g tube of the skin care cream containing the TRPV1-inhibitor 4-t-butylcyclohexanol cream (Eucerin UltraSENSITIVE®, Beiersdorf AG) was provided to the patients, who were instructed to apply it twice daily. The cream's ingredients are water, squalene, glycerin, pentylene glycol, methylpropanediol, tapioca starch, arginine HCL, cetearyl alcohol, 4-t-butylcyclohexanol (Trans-Isomer), ammonium, acryloyldimethyl-taurate/VP copolymer, sodium carbomer and caprylyl glycol. Patients were not allowed to use any other topical cosmetic or medicated drug on the face, except for the study cream.

The study consisted of an enrollment visit, a control visit after 4 weeks and a final visit after 8 weeks. A second tube was provided at the week-4 visit, and tubes were weighed at week 4 and week 8 to assess use of the cream. A total of two patients received a third tube of cream since two tubes did not suffice for the treatment period. The first visit included a standardized set of questions for age, sex, personal history of allergic rhinoconjunctivitis, bronchial asthma or atopic dermatitis, known allergies, POD duration and previous use of topical steroids or any other treatments. All three visits consisted of a physical examination, a documentation of clinical findings and adverse events, POD severity index (PODSI), subjective POD severity numeral rating scale (NRS 10) and dermatological life quality index (DLQI) scores. Patients were additionally examined for objective skin physiology parameters with Tewameter® for TEWL, Corneometer® for stratum corneum hydration (SCH), pH meter® for pH, Mexameter® for erythema, Sebumeter® for sebum level and Cutometer® for skin firmness (depth of skin suction, in mm) and elasticity (relationship between firmness and ability of skin to return to original position, expressed as a percentage). All devices are a product from Courage-Khazaka Electronic. All parameters were measured on the affected perioral area in addition to the forehead and cheek as control areas.

The study protocol was reviewed by the ethics committee of the university faculty and all participants provided written-informed consent. This study was conducted in compliance with the International Conference on Harmonized Tripartite Guidelines for Good Clinical Practice 1996, Directive 91/507/EEC, the Rules Governing Medicinal Products in the European Community, and the Declaration of Helsinki.

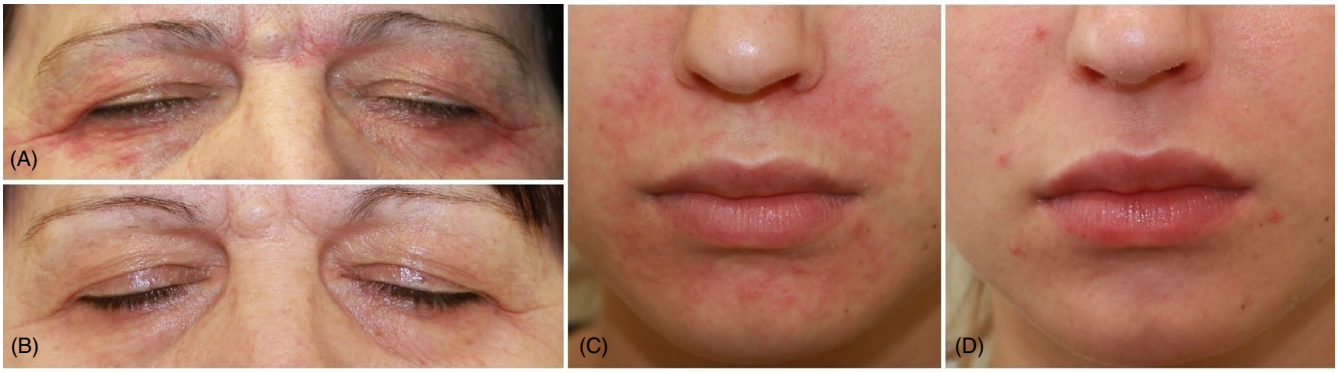


**FIGURE 1** Clinical improvement of perioral dermatitis using a cosmetic cream. First patient with moderate perioral/periocular dermatitis (POD); A, before (PODSI 3) and (B) after 8 wk of treatment (PODSI 0.5) with cream. Second patient with moderate POD; C, before (PODSI 4) and (D) after 8 wk of treatment (PODSI 1) with cream

### 2.2 | Efficacy evaluation

Our predefined, primary endpoint was to check for a significant improvement in the objective signs of POD with the perioral dermatitis severity index (PODSI) after 4 weeks (Figure 1). The PODSI represents the sum of three individual objective scores for erythema, papules, and scaling graded from 0 (none) to 3 (severe) resulting in a total PODSI score of 0 to 9.[10] Secondary efficacy variables included single items of the PODSI score, the subjective severity assessed with NRS 10, DLQI, and skin physiological parameters (TEWL, SCH, erythema, pH, sebum level, and elasticity).

### 2.3 | Adverse events

Adverse events were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) system during each visit, including their duration and severity grade (mild, moderate, or severe).

### 2.4 | Statistical analysis

Efficacy data analysis was performed for the intent-to-treat population. The data are presented as the mean together with the standard deviations. A Wilcoxon signed-rank test with 1-tailed *P*-value was used for the confirmatory analysis comparing treatment response and skin barrier function changes. The percentage change from baseline was summarized at each timepoint. All statistics were calculated using the GraphPad Prism 5 Software (GraphPad Software Inc), and visualization of data using graphs was performed using Microsoft Excel.

## 3 | RESULTS

### 3.1 | Patient characteristics

Forty-eight patients (42 women and 6 men) with a mean age of 42.4 years (19-81 years) were enrolled in the study, and 42 patients completed the treatment period. Reasons for discontinuation were noncompliance in one patient, inability to schedule the control appointment in one patient, worsening of the perioral dermatitis in one patient, and no-show of three further patients.

One-third of the patients (35%) had an atopic diathesis; 13 patients (27%) had a history of allergic rhinoconjunctivitis, three patients (6%) had a history of bronchial asthma and five patients (10%) had a history of atopic dermatitis. The duration of POD ranged from a minimum of 1 week to a maximum of 10 years. Most patients reported regular and extensive use of facial skin care products and/or make-up for months and years before the beginning of the study.

Out of the 48 recruited patients, 22 had a history of steroid use. Many readily received other medical treatments before study enrollment; topical antibiotics, pimecrolimus, or metronidazole. A minority of the patients had been treated with oral tetracyclines or tried zero therapy. The average amount of cream used was 30.93 g in the first 4 weeks of treatment, and 31.77 g were used during the second 4-week period.

### 3.2 | Treatment efficacy

The mean PODSI, the primary endpoint, was significantly reduced ($P < .0001$) from 4.71 ± 1.37 to 2.83 ± 1.75 after 4 weeks. A further significant PODSI reduction ($P < .0001$) to 1.42 ± 1.36 was observed

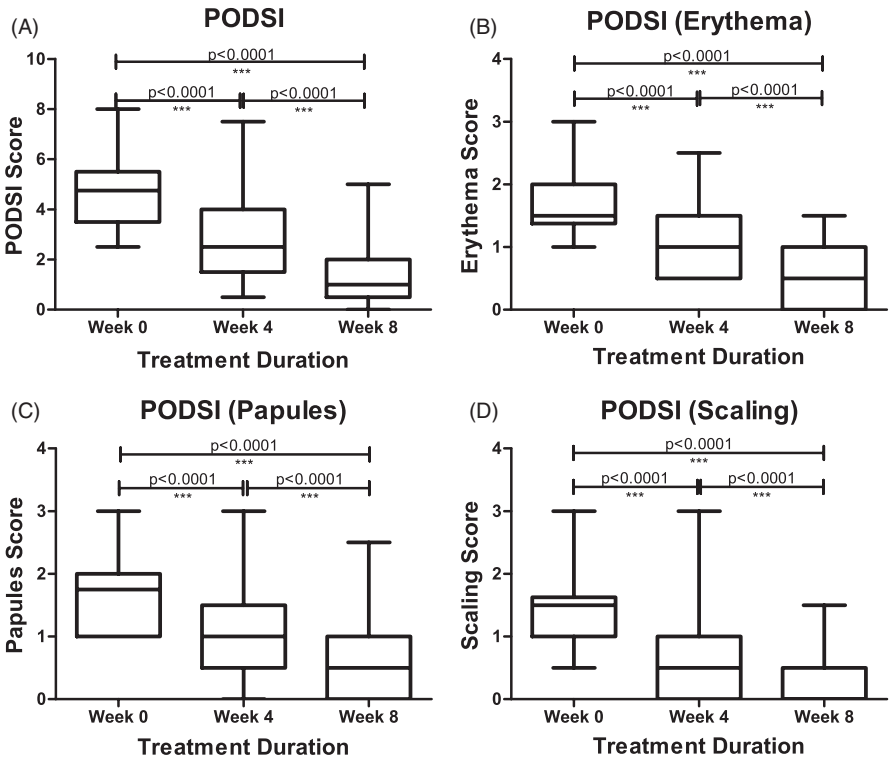


**FIGURE 2** Change of the objective signs of perioral dermatitis. Change in the objective signs of POD during 8 wk of topical skin care cream treatment in 42 patients. A, Change in the PODSI score, (B) change of the erythema component of PODSI, (C) change in the papular component of PODSI, (D) change in the squamous component of PODSI. ***Significance value of $P < .0001$

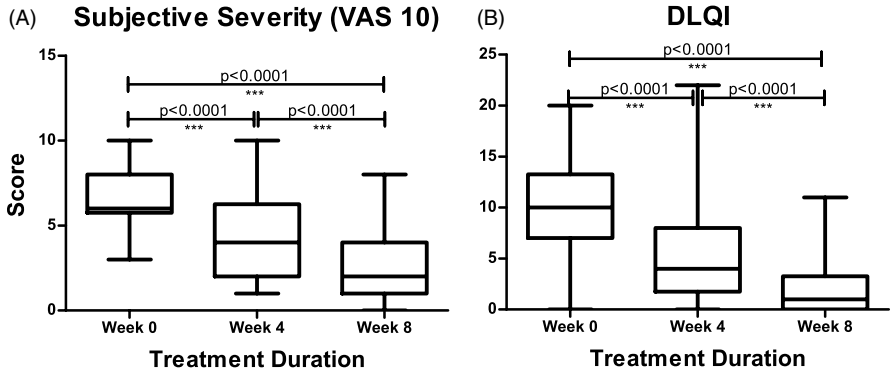


**FIGURE 3** Change in the subjective symptoms of perioral dermatitis. Change in the subjective symptoms of POD during 8 wk of topical skin care cream treatment in 42 patients. A, Change in the overall disease severity perception (numerical rating scale (NRS)), (B) change in the dermatology life quality index (DLQI). ***Significance value of $P < .0001$

after the second 4 weeks. All three PODSI elements showed a highly significant reduction over the course of 8 weeks as well; scaling showed the highest reduction (Figure 2).

The subjective aspects of POD also improved significantly during the trial period. The mean subjective disease severity on a scale from 0 to 10 (NRS 10) decreased from 6.74 ± 1.93 to 4.51 ± 2.61 after 4 weeks ($P < .0001$) and then to a final score of 2.74 ± 2.35 after four more weeks. As for DLQI, the reduction was also highly significant ($P < .0001$); during the first 4 weeks, it changed from 10.07 ± 5.21 to 5.10 ± 4.89 and to 2.19 ± 2.94 after the second 4 weeks (Figure 3).

## 3.3 | Skin physiological examination

TEWL remained unchanged in the first 4 weeks, changing from 29.36 ± 11.98 to 29.21 ± 12.61 ($P = .3308$), and then decreased to 25.45 ± 9.98 showing statistical significance ($P = .0280$) in the second 4 weeks. The most statistically significant change occurred in the stratum corneum hydration, which increased in the first 4 weeks from 39.35 ± 11.75 to 49.11 ± 12.23 ($P < .0001$). After four more weeks, it remained stable to 48.81 ± 10.47 without statistical significance ($P = .4061$). Erythema decreased over the 8 weeks period from 430.20 ± 90.50 to 406.90 ± 87.85, showing a low statistical significance ($P = .0178$). All skin pH values were within normal range; however, they decreased from 5.64 ± 0.56 to 5.41 ± 0.45 with statistical significance ($P = .0016$) after 4 weeks and remained almost constant after 8 weeks with a value of 5.48 ± 0.53 ($P = .0936$). Finally, sebum level, skin elasticity, and firmness did not significantly change over the treatment period. (Figure 4).

## 3.4 | Subgroup analyses

A correlation quotient $R^2 = 0.02271$ between the amount of cream used and PODSI improvement was determined (Figure 5A),

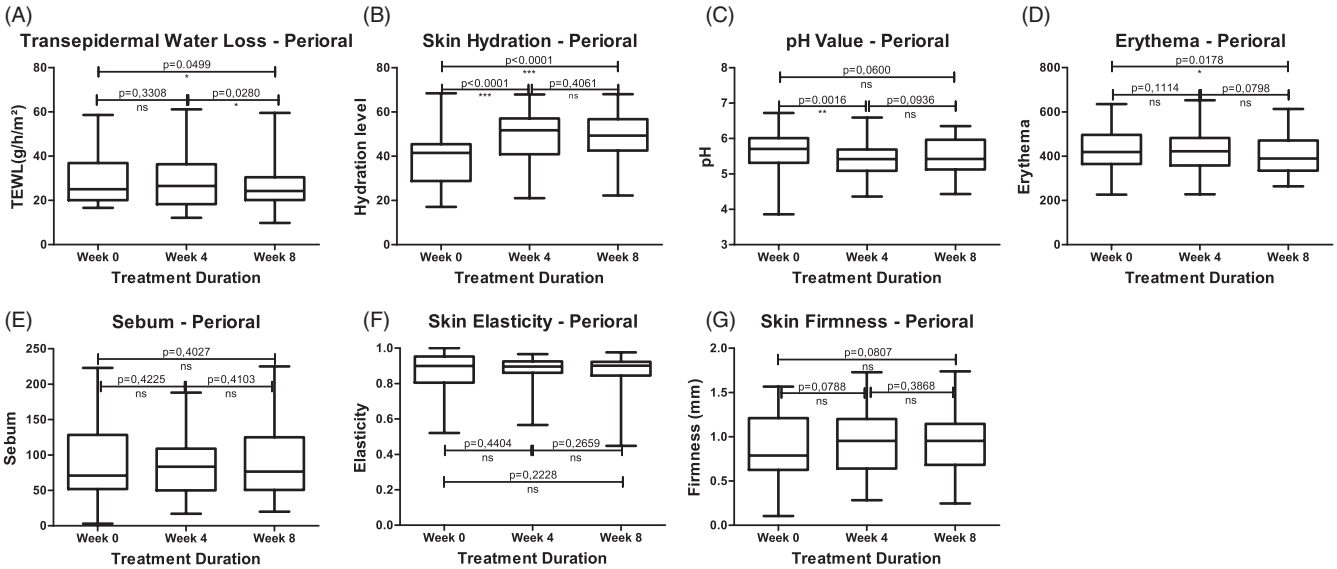


**FIGURE 4** Skin physiological changes during 8-wk treatment. Change in the different physiological parameters of the skin during 8 wk of topical skin care cream treatment in 42 patients. A, Change in the TEWL measured using Tewameter®, (B) change of the stratum corneum hydration measured using Corneometer®, (C) change in the pH measured using pH meter®, (D) change of the erythema measured using Mexameter®, (E) change of the sebum level measured using Sebumeter®, (F) change in the skin elasticity measured using Cutometer®, (G) change in the skin firmness measured using Cutometer®. *Significance value of $P < .05$, **significance value of $P < .01$, ***significance value of $P < .0001$, ns: not significant

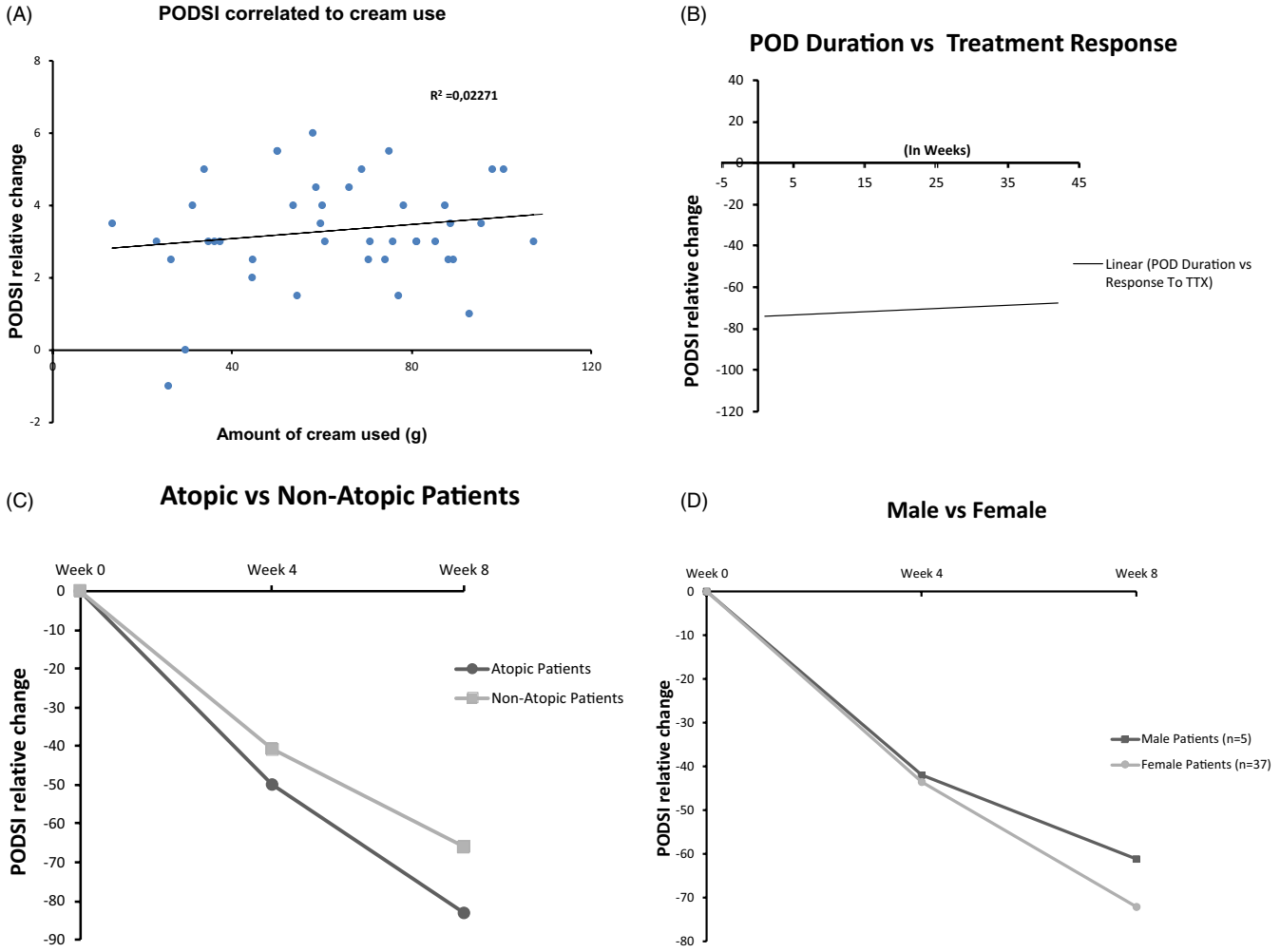


**FIGURE 5** Subgroup analyses. A, Correlation between mean PODSI relative change & amount of cream used. B, Correlation between mean PODSI relative change and POD duration before study enrollment. C, Subgroup comparison of mean PODSI relative change between atopic and nonatopic patients according to medical history. D, Subgroup comparison of mean PODSI relative change between male and female patients

without statistical significance. Another correlation was tested between POD duration and treatment response. A quotient $R^2$ = 0.0002048 was detected without statistical significance (Figure 5B).

Atopic patients were compared to nonatopic ones. After 8 weeks, PODSI mean relative change showed an 83.05% decrease with atopy and 65.96% without atopy. A *P*-value of .0381 with low statistical significance was determined (Figure 5C).

Male patients were compared to females. PODSI mean relative change resulted in 61.19% decrease with males and 72.14% with females. A *P*-value of .0781 was determined yet without statistical significance (Figure 5D).

### 3.5 | Adverse events

The cream was well tolerated by all patients. One-third of the patients complained of a mild worsening of skin tenderness and erythema in the first week of treatment.

## 4 | DISCUSSION

According to our study results, the disease course of POD improved over 8 weeks both objectively (PODSI) and subjectively (NRS 10, DLQI) with high statistical significance. The TEWL, SCH, erythema, and pH all showed improvement at the end of the treatment period. Subgroup analyses pointed out an increased treatment response in atopic POD patients, and a trend when using more cream or in female patients. No important correlation was found with medical history of POD before the study.

Objective clinical score improvement using PODSI was the primary endpoint to determine clinical response. PODSI changes over the course of 4 weeks and then of 8 weeks clearly prove that the clinical signs of POD improved. The subjective scores further support the clinical improvement of disease, since patients had fewer complaints and expressed relief in the disease's psychological burden under therapy. Other POD therapies were also previously established; topical erythromycin, topical metronidazole, and systemic tetracycline

all seem to have positive effects on the disease course. Systemic tetracycline shows a higher efficacy than the two other treatments and is thus reserved for more severe cases.[11,12] Efficacy of zero therapy has not been investigated yet. The possible side effects that patients might develop from antibiotic use, and the concern related to bacterial resistance, do not support the use of antibiotics in POD in the long-term. Appropriate skin care can thus be used long-term and serve as a promising topical therapy option for POD.

The improved values of TEWL, stratum corneum hydration, pH and erythema show an improvement of the barrier function and a successful treatment response. The measured values of this study were constantly compared to normal reference ranges determined by the company providing the devices. These predetermined data are measures of a healthy, nonlesional skin under reproducible conditions (temperature and humidity). Skin physiology devices play an important role in dermatological research and help to counteract clinician's bias.

Based on clinical experience, it is known by now that zero therapy is not well accepted by patients suffering from POD. In reality, asking patients to refrain from using all their cosmetic products and not recommending a specific therapy lead to compliance issues, especially due to the initial exacerbation phase.[5] Thus, engaging patients to use a skin-soothing cream containing 4-t-butylcyclohexanol functions simultaneously as a psychological support and a biologically active therapy. Instead of overhydrating the skin and re-entering the hydration-dryness vicious circle, physicians should develop a trustful doctor-patient relationship and deliver clear instructions regarding the amount and frequency of cream used.[13] On the molecular level, TRPV receptors are known to activate pain perception under inflammatory conditions in the skin, since they are widely distributed in different components of the skin such as nerves and epithelial cells.[14,15] Firstly, ameliorating symptoms of POD patients is a substantial target of therapy and secondly, the subjective disease improvement noted by patients leads to a higher compliance and remission rate.

Influencing factors of treatment response were investigated by subgroup analysis. Patients with an atopic history responded significantly better to the treatment, whereas all other subgroup analyses showed trends but gave insignificant results. It might be hypothesized that the observed results are caused by an increased cutaneous damage at baseline, because women use cosmetic products more excessively than men do, and atopic patients readily have subclinical inflammation and increased TEWL.

Our unblinded, single-armed, prospective trial could have been designed differently by including a control group of patients using a vehicle formulation without 4-t-butylcyclohexanol and by blinding the two groups. It would have answered different questions and warranted further investigations.

The skin physiological parameters which were measured under standardized and reproducible conditions with calibrated and sensitive devices correspond to the clinical improvement under treatment, thus drawing a comprehensive picture overall.

To sum up, this study provides evidence for the clinical efficacy of a skin care cream with a TRPV1 inhibitor as an active ingredient in POD treatment. Objective, subjective POD scores and skin's physiological parameters clearly improved during the 8-week treatment period. A 4-t-butylcyclohexanol cream could be a clinically useful treatment option for POD, especially due to the absence of side effects and the lack of limitations in the duration of treatment.

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