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ORIGINAL ARTICLE

Efficacy and Safety Results of a Drug-Free Cosmetic Fluid for Perioral Dermatitis: The Toleriane Fluide Efficacy in Perioral Dermatitis (TOLPOD) Study

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Background: Perioral dermatitis (POD) is a common inflammatory skin disease without standard therapy. **Objective:** We sought to evaluate the clinical value of a soothing fluid for the treatment of POD. **Methods:** We included 51 patients with POD in this 8-week clinical trial. The Toleriane Fluide Efficacy in Perioral Dermatitis (TOLPOD) study had an open-label design and involved twice-daily application of Toleriane Fluide, a soothing cosmetic fluid. Clinical assessment of POD was performed with a predefined questionnaire including the POD severity index (PODSI). Control visits were made after 4 and 8 weeks of treatment. **Results:** The results were compared with those of a historical control group treated with a vehicle cream. Patients treated with the soothing fluid showed a continuous and significant improvement of the PODSI over time. The improvement of PODSI observed with the soothing fluid was better, but not significantly better, than that observed in the historical controls. In addition, the subjective complaints of patients such as disease burden, itching, distension of the skin, and appearance improved during treatment. **Conclusion:** A soothing fluid could be a clinically useful treatment option for POD. **(Ann Dermatol 26(4) 462～468, 2014)**

-Keywords-
Clinical trial, Perioral dermatitis, Perioral dermatitis severity index score, Soothing fluid, Subjective severity score, Zero therapy

INTRODUCTION

Perioral dermatitis (POD) is a clinically distinctive reaction pattern of the skin characterized by a burning sensation, and sometimes, itchy perioral erythematous papules. The term "perioral dermatitis" was introduced in 1964 by Mihan and Ayres[1] on the basis of a case series of 21 patients. This commonly occurring disorder, typically seen in young and middle-aged women, is often resistant to therapy[2]. Its objective signs and subjective symptoms lead to a remarkable reduction in the quality of life for many patients.

Although the pathogenesis of POD remains unclear, some factors are considered relevant. POD seems to be an intolerance reaction of facial skin to repetitive irritation. Overhydration of the skin caused by the excessive use of occlusive moisturizing emollients may result in the destruction of the skin barrier function. Increased transepidermal water loss leads to sensations of tension and skin dryness, which prompts patients with POD to increase their use of topical products. This creates a vicious circle of irritation, feeling of tenderness, dry skin, and further use of moisturizers[3]. Many patients with POD are atopic, which in the case of atopic eczema is associated with a reduced skin barrier function by itself[4]. An imbalance of the physiological skin flora caused by the excessive use of cosmetics may also play a role. On clinical grounds, the intermittent (ab-) use of potent topical steroids is an esta-

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blished risk factor for POD[5].

Treatment of POD can be a frustrating experience for patients and doctors. The choice of a treatment regimen is based more on expert opinions than on clinical trials[6]. The first guideline for POD treatment comments on several treatment options but does not recommend a single "gold standard" therapy[6]. The discontinuation of all topical agents (or zero therapy) is an established approach; however, the initial exacerbation of POD regularly hinders patient compliance[6]. Topical antibiotics such as metronidazole and erythromycin or topical pimecrolimus are established treatment options despite having a possible rebound effect. Systemic agents such as tetracycline or erythromycin derivatives are recommended in severe or recurrent cases[6].

As patients often do not accept zero treatment, we searched for a nonirritative, indifferent cosmetic agent for POD therapy by using a "proof-of-concept" approach. This Toleriane Fluide Efficacy in Perioral Dermatitis (TOLPOD) study was performed to clarify whether the twice-daily application of a thin layer of cosmetic soothing fluid will be well tolerated and clinically effective for the treatment of POD. In addition, we were interested in a subgroup analysis of several risk factors (e.g. atopic diathesis, steroid pretreatment, or disease severity at inclusion) on the clinical efficacy of the soothing fluid.

MATERIALS AND METHODS

Patient population

The inclusion criterion was patients with a clinically diagnosed POD with a minimum POD severity index (PODSI) of ≥ 2.5 irrespective of the type of pretreatment. The exclusion criteria were underage, pregnant, or breastfeeding patients, or patients with a planned medical drug treatment for their POD. Patients with other skin diseases of the face that might interfere with grading were also not included. We included in the trial 51 eligible patients, consisting of 4 men and 47 women aged 19～78 years, with clinically diagnosed POD and a mean PODSI of 5.87. The study protocol was reviewed by the ethics committee of our faculty (Proj.-Nr. 365-10) and all participants provided written informed consent. This study was conducted in compliance with the International Conference on Harmonisation 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.

Study design

This was a single-center, open-label, unblinded, 8-week study with a historical control group. There was no screening or washout phase. The patients were administered with the soothing fluid (Toleriane Fluide; L'Oreal Germany, Dusseldorf, Germany) containing dipropylene glycol, ethylhexylglycerin, squalane, carbomer, caprylyl glycol, glycerin, sodium hydroxide, and water twice daily for 8 weeks. The study consisted of an enrollment visit, a control visit after 4 weeks, and a final visit after 8 weeks. Each visit included a survey, a physical examination, and documentation of clinical findings and adverse events. We recorded clinical parameters such as patient age, sex, personal history of allergic rhinoconjunctivitis, asthma bronchiale or atopic dermatitis, known allergies, previous use of topical steroids, or other pretreatment for the POD. The amount of fluid used by the patients was assessed by weighing the used fluid tubes that the patients had to bring at every visit. Patients were advised to stop using any topical drugs or cosmetics on their face, with the sole exception of the soothing fluid.

Efficacy evaluation

Our primary objective was to measure the objective signs of POD severity during the 8-week treatment with the soothing fluid (Fig. 1). The predefined endpoint was a significant improvement of POD severity after 4 weeks, as assessed with the PODSI[7]. This index calculates the sum of 3 individual objective scores for erythema, papules, and scaling graded from 0 (none) to 3 (severe) resulting in a total PODSI score of 0～9. Secondary efficacy variables

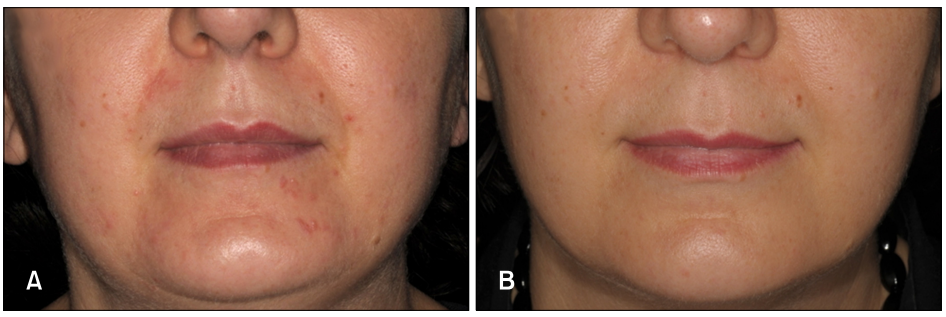

Fig. 1. Clinical improvement of perioral dermatitis with a soothing fluid. A patient with moderate perioral dermatitis (POD). (A) Before (POD severity index [PODSI] 5) and (B) after 8 weeks of topical treatment (PODSI 0) with a soothing fluid.

included single items of the PODSI score, as well as the subjective severity, itching, distension of the skin, and appearance, as assessed with a visual analogue scale (VAS) of 0～10.

To approximately compare the efficacy of the soothing fluid with the published data, we visualized the TOLPOD data together with historical, published data from a vehicle-controlled study with pimecrolimus cream (1%; Elidel; Novartis, Nuremberg, Germany) and a pimecrolimus-free cream base that also used the PODSI as the outcome measure[8]. The composition of the vehicle cream in this pimecrolimus cream (1%) trial was identical to that of the commercial pimecrolimus cream (1%), with the exception of the missing active ingredient, pimecrolimus[8].

Adverse events

Adverse events were recorded by using the Medical Dictionary for Regulatory Activities (MedDRA) system during each visit, including their duration, severity grade (mild, moderate, or severe), possible relation to the soothing fluid (suspected/not suspected), and the action(s) taken. Any pregnancy occurring during the study was aimed to be reported and followed-up to determine the outcome.

Statistical analysis

Efficacy data analysis was performed for the intent-to-treat population. The data is presented as the mean together with the standard deviations. A t-test with a 1-tailed *p*-value at an experimental level of $\alpha = 0.05$ was used for the confirmatory analysis comparing treatment response, and a t-test with 2-tailed *p*-values was used for descriptive analyses. Summary statistics of the subjective severity score and the other subjective symptoms were presented at each time point for each symptom. The percentage change from baseline was summarized in a similar manner. To compare the data of the TOLPOD study with the historical data, an unpaired t-test with a *p*-value of < 0.05 and a Wilcoxon signed rank test with *p*-values of 0.5 and 1.0 were performed. All statistics were calculated using the GraphPad Prism 5 Software (GraphPad Software Inc., La Jolla, CA, USA).

RESULTS

Study population

Fifty-one Caucasian patients (4 men and 47 women) with a mean age of 39.3 years (range, 19～78 years) were included in the study, and 39 patients completed the treatment period. Reasons for discontinuation were noncompliance in 3 patients (use of restricted topical cosmetics or medication), inability to schedule the control appointment in 6 patients, and complete loss to follow-up in another 3 patients.

Most of the patients (n=27, 53%) had an atopic diathesis; 4 patients (8%) had a history of bronchial asthma; 7 patients (14%) had a history of atopic eczema; and 9 patients (18%) had a history of allergic rhinoconjunctivitis. Immediate-type hypersensitivity, mostly to aeroallergens, was reported in 17 patients (33.3%), whereas 4 patients (7.8%) had a history of delayed-type allergy to contact allergens. On an average, most patients experienced POD for 36.2 weeks, and 20 patients (39.2%) experienced previous episodes of POD, with an average of 5 recurrences. All patients had cultivated an intensive facial skin care regimen before their study enrollment, with a minimum of 2 different skin care products used per patient per day.

Most patients (n=42, 82%) had used medicated therapy before study enrollment, which consisted of topical antibiotics (n=20, 39%) or topical pimecrolimus (n=6, 12%). A minority of the patients had been treated with oral tetracycline (n=2, 4%) or tried zero therapy (n=6, 12%) before enrollment. Some patients (n=9, 18%) had used topical steroids before inclusion, whereas only 10 patients (20%) had not undergone any treatment to improve their skin condition.

The amount of soothing fluid used was 21.4 ± 8.4 g in the first 4 weeks of treatment, and approximately equal amounts of 20.4 ± 8.0 g were used during the second 4-week period. On the basis of the current data from the German market, the monthly cost for this treatment is an average of < 7 Euro per month.

Efficacy of the soothing fluid over time

The efficacy of the soothing fluid in POD treatment was constant over the entire treatment period. The mean PODSI, the primary endpoint, significantly ($p < 0.0001$) reduced from 5.87 ± 1.40 to 3.73 ± 1.50 after 4 weeks. A further significant ($p < 0.0001$) PODSI reduction to 2.51 ± 1.40 was observed after 8 weeks. The scaling component showed the highest reduction of all single objective parameters of the PODSI (Fig. 2).

The subjective aspects of POD also improved significantly during the trial period. The mean subjective disease burden decreased from 6.3 ± 2.4 (VAS) to a mean score of 4.4 ± 2.4 (VAS) after 4 weeks (a reduction of 30%), and decreased again to a final value of 3.4 ± 2.2 (VAS) after 8 weeks (final reduction of 46%). All other subjective symptoms such as itching, distension of the skin, and subjective appearance also improved continuously and significantly (Fig. 3).

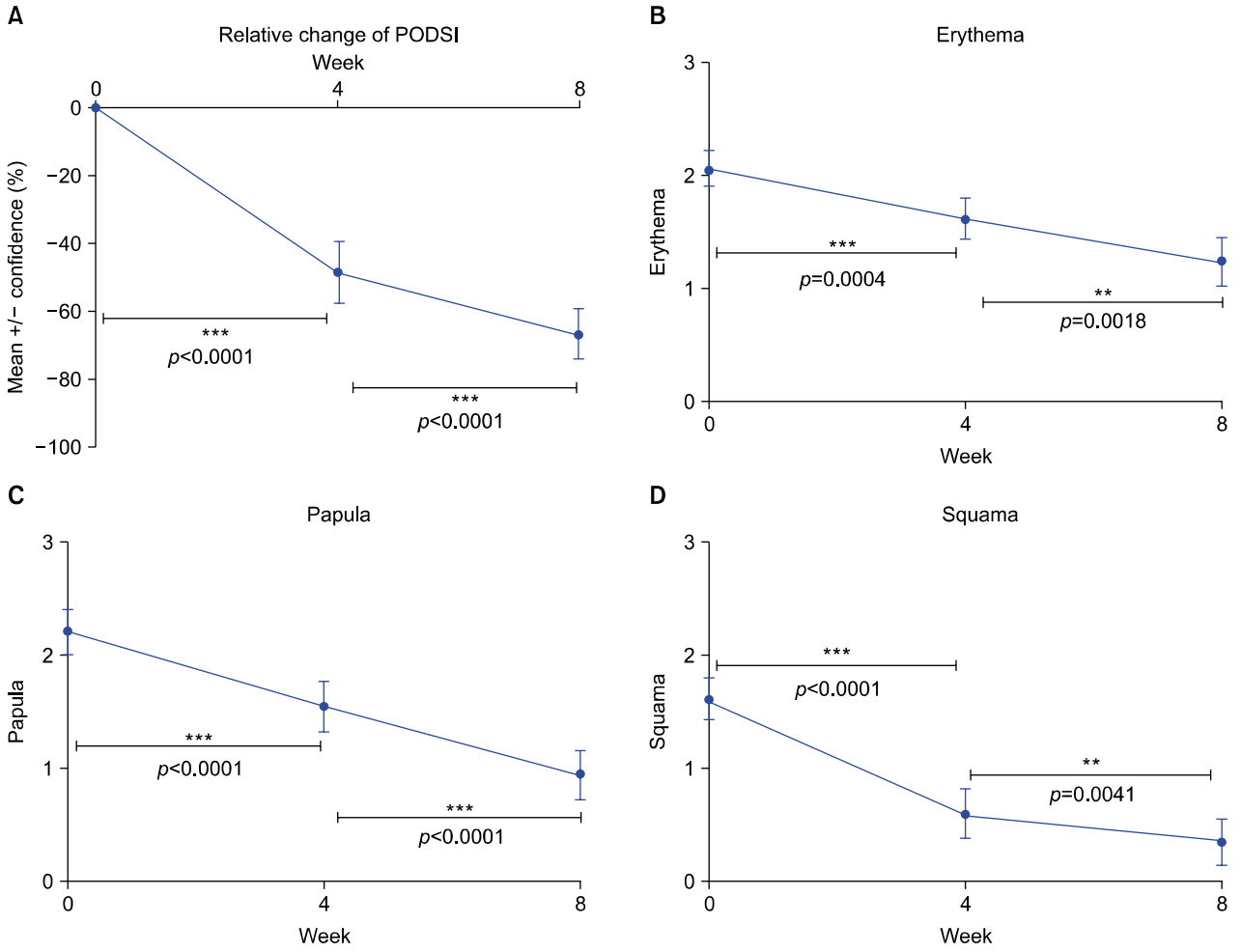

Fig. 2. Change of the objective symptoms of perioral dermatitis (POD) during the POD severity index (PODSI) trial. Change of the objective signs of POD during 8 weeks of topical soothing fluid treatment in 39 patients. (A) Change of the PODSI score[7], (B) change of the erythema component of PODSI, (C) change of the popular component of PODSI, (D) change of the squamous component of PODSI. **Significance value of $p<0.01$, ***significance value of $p<0.0001$.

Efficacy in clinical subgroups of POD

In the subgroup analysis, patients with nonatopic POD showed better improvement than patients with atopic POD; however, the difference in PODSI was not statistically significant (Fig. 4A). Patients with POD reporting steroid pretreatment or any other pretreatment showed almost the same reduction of their PODSI than those patients without a history of pretreatment. Patients with long-lasting disease and frequent recurrences showed a reduction in their PODSI similar to those with recently diagnosed disease (data not shown).

A moderate use of the soothing fluid seemed favorable over intensive use in terms of treatment outcome (Fig. 4B), as there was an inverse correlation of soothing fluid use and PODSI improvement that almost reached statistical significance ($p=0.066$).

Efficacy of the soothing fluid compared with historical data

As the TOLPOD study was designed without a control group, direct comparison with another treatment regimen is not possible. Fortunately, there are historical data published from clinical trials with pimecrolimus cream (1%) that also used the PODSI as the outcome measure and included a control group[8]. The placebo group of that study consisted of 20 patients, 18 of whom completed the 4-week treatment period. The age (42 ± 17 years, range 20～65 years) and ethnicity of the 95% Caucasian women of that trial are also comparable to our study group. There was no significant difference in age, sex, race, or disease severity at baseline on statistical analysis between the 2 groups. During the first 4 weeks, both groups showed a significant improvement of the PODSI. In the soothing fluid group, the PODSI reduced by 48.37% from 5.9 ± 1.4 to 3.7 ± 1.5. In the historical vehicle group, the PODSI

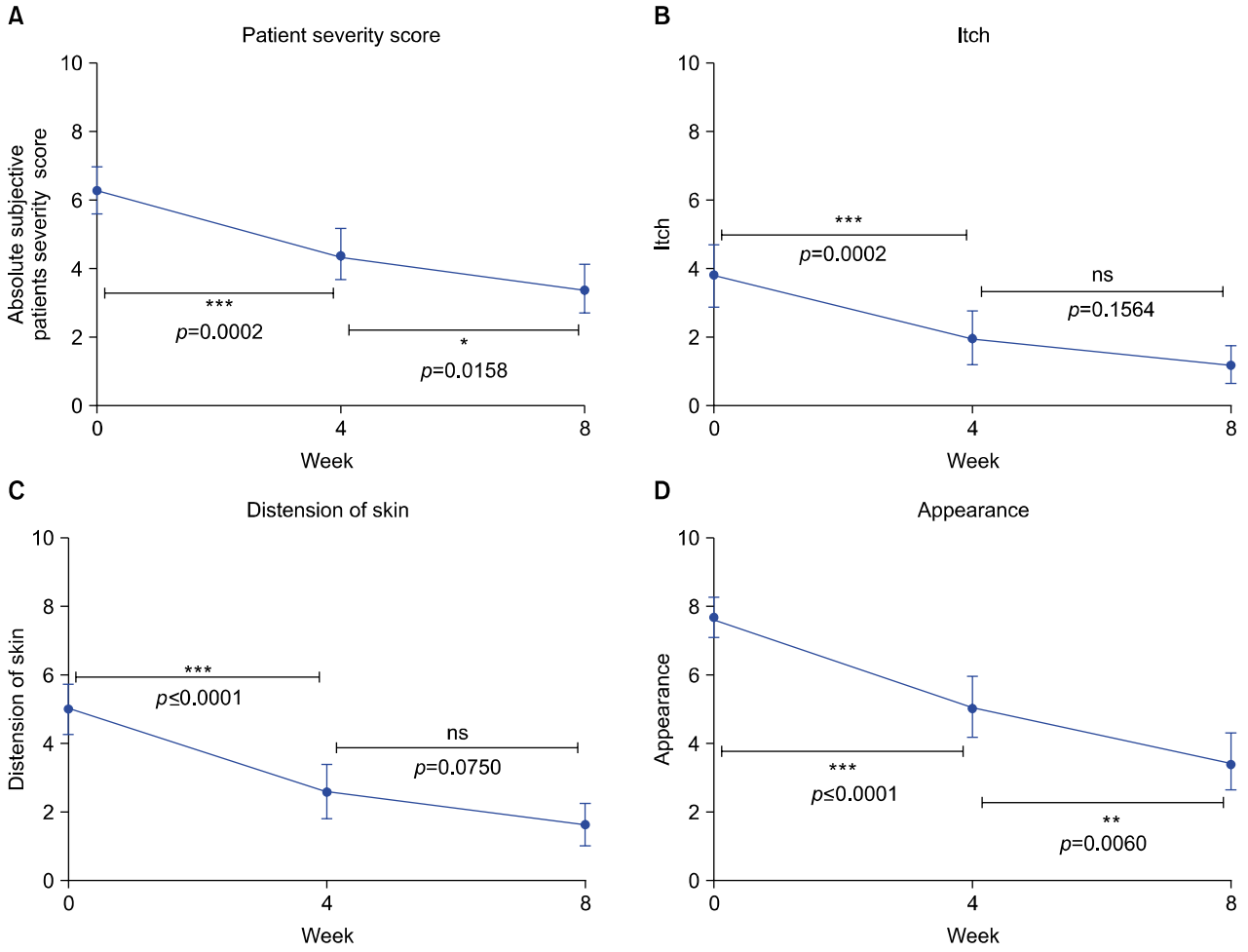

Fig. 3. Change in the subjective symptoms of perioral dermatitis (POD) during during the POD severity index trial. Change in the subjective symptoms of perioral dermatitis during 8 weeks of topical soothing fluid treatment in 39 patients. (A) Change in the overall disease severity perception (visual analogue scale [VAS]), (B) change in itch perception (VAS), (C) change in perception of skin distension (VAS), (D) change in appearance as a subjective impression (VAS). *Significance value of $p<0.05$, **significance value of $p<0.01$, ***significance value of $p<0.0001$. ns: not significant.

reduced by 43.4% from 4.6 ± 1.1 to 2.6 ± 1.5. A significant difference between the 2 groups could not be determined. However, the group treated with the soothing fluid showed better improvement (Fig. 4C).

Adverse events

No adverse events were observed during the entire study period. None of the patients complained about subjective adverse effects such as irritation or a burning sensation. During the entire treatment period, the soothing fluid was well tolerated by the participants. No patient became pregnant.

DISCUSSION

Our TOLPOD study provides evidence for the beneficial effects of a soothing fluid in patients with POD. This includes significant improvement of the objective signs as assessed by PODSI, as well as subjective symptoms including disease burden, itching sensation, distension of the skin, and subjective appearance. Patients with atopic and nonatopic POD, newly diagnosed patients and patients with chronic POD, as well as steroid-pretreated patients and non-steroid-pretreated patients with POD all responded more or less equally well to the treatment. The application of low amounts of the fluid seemed more efficient than using higher amounts. The initial proof of efficacy of a new therapy should be shown against an untreated control. Furthermore, the only option in performing high-level evidence clinical trials is a randomized, double-blinded, placebo- or otherwise controlled approach. The optimal study design of a POD trial is an unsolved problem. The only way to blind patients to a topical formulation is to use another topical formulation,

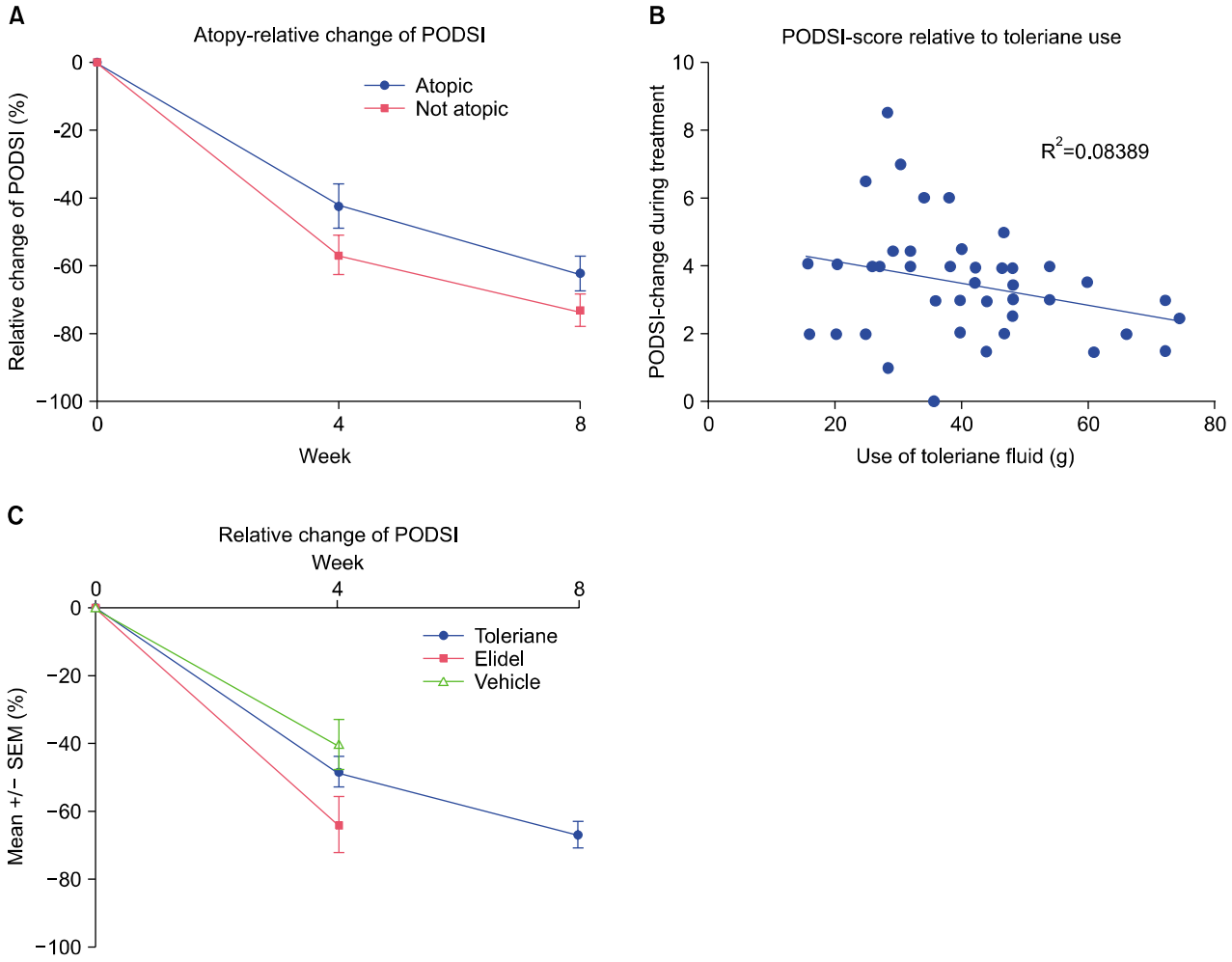

Fig. 4. Subgroup analysis of patients with nonatopic perioral dermatitis (POD), clinical improvement correlated with the amount of fluid use, and comparison with a historical control group. (A) Patients with nonatopic POD showed a tendency to improve faster and better with the soothing fluid than patients with POD having an atopic diathesis ($p=0.7$). (B) Individual improvement of the POD severity index (PODSI) score in 39 patients plotted against the individual amount of soothing fluid (g) used during the 8-week study period. $R^2=0.08389$. (C) Time course of PODSI in 39 patients with POD treated for 8 weeks with a soothing fluid, as well as a historical control of 20 patients treated for 4 weeks with a cream base and untreated for another 4 weeks[8]. There was better improvement with the soothing fluid; however, the differences observed were not significant. Comparison with historical data from Oppel et al.[8] showed that the soothing fluid has nearly the same positive effect on POD as pimecrolimus cream (1%) after 4 weeks of treatment.

which is usually the vehicle base without the active ingredient. "Zero therapy" is, in the case of POD, an established treatment itself, and patients cannot be blinded to this type of treatment. As we have studied a cosmetic product and not a medicated treatment, a drug-free basis is not possible. Therefore, there is an inherent dilemma of both imperfect blinding and imperfect control treatment in efficacy trials for POD. This dilemma brought us to use historical control data from a previous trial that we had conducted, using a similar trial setting and outcome parameters.

Patients treated with the soothing fluid showed slightly better efficacy results than the historical patient group treated with the Elidel cream base; however, this difference was small and not statistically significant. The Elidel cream is richer in fat, and its water content is lower than that of the soothing fluid, which typically defines the character of a cream in contrast to that of a fluid. Perhaps this creamy texture provides a moisturizing and slightly occlusive effect on the skin, which is known to have negative effects on POD. The soothing fluid seems to be more inert than the vehicle cream. Pimecrolimus cream (1%) is a well-recognized treatment for POD and recommended in the current guidelines for POD[6]. As there are no clinical trial data comparing pimecrolimus cream (1%) with a soothing fluid, we decided to compare published

historical data of both treatment regimens. The improvement seen after 4 weeks of pimecrolimus cream (1%) treatment is slightly better than with the soothing fluid[8], which may be attributed to the anti-inflammatory properties of the calcineurin inhibitor, pimecrolimus.

The active principle of the trial may be the application of the soothing fluid, the avoidance of use of any additional cosmetics, or both. Zero therapy is known to be effective in the treatment of POD[6]. However, as a disadvantage, the avoidance of all cosmetic products often leads to a flare-up of POD with severe distension of the skin. This reaction dramatically reduces patient compliance. It is well known that strict control improves patients' compliance. Particularly in POD, good compliance is important for a successful treatment. Although an intensive, alternating inappropriate use of cosmetics may lead to the development of POD[9], a controlled twice-daily application of an inert topical agent like the soothing fluid may prevent "overcare" and has been beneficial in our clinical trial setting. Zero therapy, although attractive on theoretical grounds, may not be feasible for many patients in clinical reality. The use of a soothing fluid may be bifunctional. On the one hand, the inert topical agent may stabilize the barrier function of overhydrated skin. On the other hand, there may be a behavioral component in the well-accepted substitution of questionable cosmetics with an inert topical agent such as a soothing fluid.

Another established therapy in clinical practice for the treatment of POD is topical erythromycin. A study published in 1993 compared topical erythromycin ointment with the systemic use of tetracycline, and found that both treatments worked equally well[10]. There is no published study directly comparing the effects of topical erythromycin, topical pimecrolimus, and soothing fluid. However, long-term application of topical antibiotics is generally not recommended because of the theoretical concern about antibiotic resistance development. A soothing fluid could be used longer if clinically needed, without this theoretical concern; however, our trial has not addressed the question of whether there is need for long-term use at all.

In conclusion, this study provides evidence for the clinical efficacy of a soothing fluid in POD treatment. Both objective and subjective symptoms of POD improved significantly during the 8-week study period. A soothing fluid could be a clinically useful treatment option for POD, especially as there are no known adverse effects reported thus far.

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