

Combination of a Topical Anti-Inflammatory Drug and a Moisturizer, Both with a Lamellar Structure Containing Synthetic Pseudo-Ceramides, for the Treatment of Patients with Mild-to-Moderate Atopic Dermatitis

Keita Okoshi¹, Shotaro Ito¹, Megumi Matsuoka¹, Yoshinori Kinugasa¹, Eri Shimizu², Kosei Tanaka², Joji Okada³, Takahiro Nishizaka¹, Azumi Nagasawa¹, Tsuyoshi Seki¹, Makoto Iijima¹, Masatoshi Abe⁴, Osamu Nemoto⁴

¹Human Health Care Products Research, Kao Corporation, Tokyo, Japan; ²Analytical Science Research, Kao Corporation, Tochigi, Japan; ³Skin Care Products Research, Kao Corporation, Tokyo, Japan; ⁴Sapporo Skin Clinic, Sapporo, Japan

Correspondence: Azumi Nagasawa, Human Health Care Products Research, Kao Corporation, 2-1-3, Bunka, Sumida-ku, Tokyo, 131-8501, Japan, Tel +81-3-5630-7690, Fax +81-3-5630-9342, Email nagasawa.azumi@kao.com

Purpose: Atopic dermatitis is characterized by chronic inflammation and dryness accompanied by severe itching. The combined use of moisturizers and topical anti-inflammatory drugs is essential for alleviating atopic dermatitis. We have developed a topical anti-inflammatory drug with a steroid and a moisturizer with heparinoid, both in lamellar structure-based formulations containing synthetic pseudo-ceramides. Here, assessed the efficacy of this combination in the treatment of atopic dermatitis.

Methods: We included 22 patients with mild to moderate atopic dermatitis and subjected them to a seven-week treatment with the test formulations, followed by a four-week post-treatment period.

Results: Clinical findings and the quality of life of participants remarkably improved after one week of treatment. Furthermore, skin hydration and transepidermal water loss considerably improved at weeks one and three, respectively. The Cer [NP]/[NS] ratio, an indicator of epidermal turnover, substantially increased during the treatment period and remained elevated even thereafter. The improvement in stratum corneum function was distinctive in participants with lower barrier function.

Conclusion: These findings indicated that the combined use of the anti-inflammatory drug and moisturizer, both in lamellar structure-based formulations, is effective in treating atopic dermatitis in patients with fragile barrier function.

Keywords: base formulations, lamellar structure, steroid, heparinoid, barrier function, TEWL

Introduction

Atopic dermatitis (AD) is a complex disease characterized by chronic inflammation accompanied by intense itchiness.¹ Scratching behavior is induced by intense itchiness, which can disrupt the skin barrier. Compromised barrier function results in moisture loss and dehydration as well as increased invasion of external stimuli (allergens) and subsequent inflammation. This creates a cycle wherein itchiness is aggravated, leading to further deterioration of symptoms (itch-scratch cycle).^{2,3} Chronic inflammation exacerbates the skin color of patients,⁴ thus impacting their psychological well-being due to the associated changes in appearance.⁵

The stratum corneum (SC) plays a crucial role in maintaining the skin barrier function,⁶ preventing water loss from within the skin and allergen entry.⁷ These functions are imparted by the intercellular adhesion between keratinocytes and intercellular lipids. Ceramide, a sphingolipid composed of sphingosine and fatty acid, is a major component of intercellular lipids. It forms a lamellar structure wherein layers of lipids and water molecules overlap regularly.^{8,9} The

skin of patients with AD exhibits abnormal turnover due to chronic inflammation.¹⁰ Compared to that of individuals with healthy skin, the stratum corneum of patients with AD contains less ceramide content,¹¹ exhibiting an immature state with a low ratio of NP to NS type ceramide in the stratum corneum (Cer [NP]/[NS] ratio), which is an indicator of epidermal turnover.¹² As a result, the skin of patients with AD loses its barrier function, affecting both water retention and the ability to prevent allergen entry.^{7,13}

The use of moisturizers along with topical anti-inflammatory drugs is central to the treatment of AD patients.^{14,15} Heparinoid, which belongs to the mucopolysaccharide family, is used as a moisturizer because of its high capacity to absorb water and moisture. On the other hand, the compromised stratum corneum also makes normalizing barrier function a priority.¹⁶ Barrier repair therapy, which is an approach that replenishes intercellular lipid components such as ceramide, is effective in maintaining a healthy SC in patients with AD.^{16,17} Ceramides, pseudo-ceramides (synthetic compounds similar to ceramide in the stratum corneum), and ceramide precursors have been reported to be effective against AD symptoms such as dry skin.^{18–22} Recently, we evaluated a steroid formulation containing synthesized pseudo-ceramide (SLE: *N*-(3-hexadecyloxy-2-hydroxypropyl)-*N*-2-hydroxyethyl hexadecanamide) and a steroid, which comprised a lamellar structure that mimics intercellular lipids. We showed that although the anti-inflammatory effect was equivalent to that of a formulation without a lamellar structure, the changes in skin hydration and transepidermal water loss (TEWL) were significant.²³ Furthermore, we found that a formulation containing synthetic pseudo-ceramides and a heparinoid that formed a lamellar structure after application and drying exhibited physical barrier function, effectively inhibiting allergen permeation.²⁴ Our assessment of the above-mentioned heparinoid formulation during AD remission revealed notable improvements in skin hydration and a reduction in the TEWL, accompanied by alleviation of itchiness. Taken together, these observations demonstrated that steroid and heparinoid formulations with a lamellar structure exhibit greater efficacy as therapeutic agents for AD than formulations without a lamellar structure. Based on these observations, the combination of a formulation that forms a lamellar structure with drug treatment and skin care could effectively improve SC function while preventing allergen entry. However, such a study has not been undertaken yet.

Here, we conducted a clinical study to verify the efficacy of a combination of topical anti-inflammatory drug with steroid and topical moisturizer with heparinoid (both of which form a lamellar structure after application) for the treatment of mild to moderate AD.

Materials and Methods

Study Design

This clinical study was conducted as a single-arm, open-label study. The study protocol was approved by the Review Board of Kao Corporation (Tokyo, Japan) and the Medical Corporation Kojinkai Sapporo Skin Clinic (Sapporo, Japan) (UMIN registration no. 000031190). This study complied with the basic ethical principles set out in the Declaration of Helsinki. All the participants provided informed consent prior to participation in the study.

After a 1-week washout period with topical agents prohibited, the test formulations were applied for 7 weeks, with a 4-week post-treatment period (Figure 1). The 7-week treatment period was as follows: in week 1, the steroid and heparinoid formulations were applied together twice a day; from week 2 to week 7, the heparinoid formulation was generally used twice a day, but combined use with the steroid formulation was permitted when symptoms worsened. The amount of formulation used complied with the fingertip unit, and participants were allowed to use their own topical formulations during the post-treatment period. Efficacy and safety assessments were conducted at weeks 0, 1, 3, 5, 7, and 11 (Figure 1). The study was conducted from February to May 2018 in Hokkaido, Japan.

Study Participants

Dermatologists screened Japanese male and female patients with AD having mild to moderate skin eruptions on their arms. Of the 33 participants, 23 individuals aged 25–48 years participated in the study.

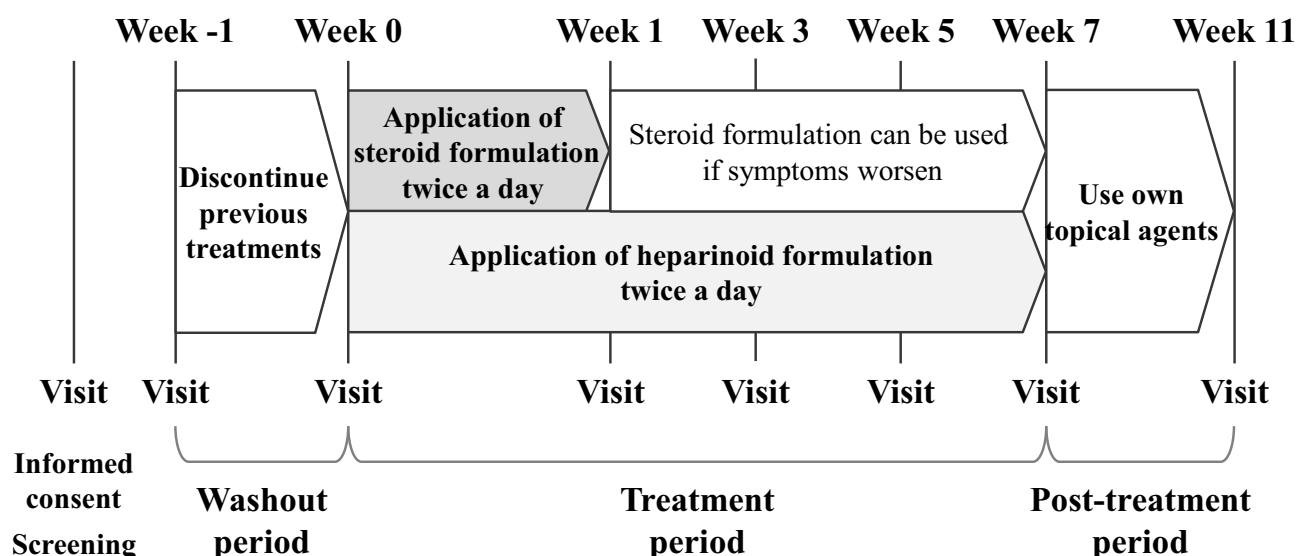


Figure 1 Study design.

Notes: After washout (week 1), the test formulations (steroid and heparinoid) were administered twice a day for one week. Thereafter, the heparinoid formulation was applied twice a day for six weeks. Moreover, steroid formulation use was also permitted depending on the skin condition of participants. Thereafter, the participants used their usual formulations for four weeks (post-treatment period).

Materials

The steroid formulation was an oil-in-water (O/W) cream formulation with 0.15% prednisolone valerate acetate (PVA) and 3% synthetic pseudo-ceramide. The other components included cetyl alcohol, stearyl alcohol, polyoxyethylene sorbitan monostearate, sorbitan monostearate, glycerin, and water. The heparinoid formulation was an O/W cream formulation containing 0.3% heparinoid and 2.5% synthetic pseudo-ceramide, along with other components such as stearyl alcohol, stearyl monoglyceride, glycerin, and water.

Efficacy/Safety Assessment and Skin Measurements

The AD severity, dryness, erythema, and scratch marks at the test site (upper arm) were scored by a dermatologist on a scale of 0–4. The severity was scored based on the severity classification of atopic dermatitis by the Japanese Dermatological Association (simple method):²⁵ none, 0; slight, 0.5; mild, 1; between mild and moderate, 1.5; moderate, 2; between moderate and severe, 2.5; severe, 3; between severe and profound, 3.5; profound, 4. Dryness, erythema, and scratch marks were scored according to the following conditions: none, 0; between none and slight, 0.5; slight, 1; between slight and mild, 1.5; mild, 2; between mild and moderate, 2.5; moderate, 3; between moderate and severe, 3.5; and severe, 4.

All adverse events during the study period were recorded, and severity was judged by a dermatologist. All instrumental measurements were conducted in an air-conditioned room at $20 \pm 2^\circ\text{C}$ and $40\% \pm 5\%$ relative humidity after acclimatization for 20 min. The same location (inside the forearm) was measured each time, aided by a transparent sheet indicating the measurement site for each participant. Skin color (a^*) and melanin content in the forearm were measured using Antera 3D (Miravex, Ireland). TEWL in the forearm was measured using a Tewameter TM300 (Courage + Khazaka Electronic, Koln, Germany). The moisture content of the SC on the forearm was measured using SKICON-200EX (IBS, Hamamatsu, Japan).

Ceramide Analysis

SC specimens were sampled from the forearm via the tape-stripping method at baseline (week 0) as well as at the end of weeks 7 and 11. Five consecutive tapes using polypropylene tape (465#40; Teraoka Seisakusho; Tokyo, Japan) were collected from inside of the forearm, and part of each SC-stripped tape was used for ceramide analysis, as previously described.²⁶ The SC-stripped tapes were stored at -20°C until lipid extraction. Each SC-stripped tape was cut into two

equal pieces; one was used for lipid extraction, and the other for protein extraction. One piece was immersed in methanol and sonicated. Extracted lipids were dried, and re-dissolved in chloroform/methanol/2-propanol (2/9/9). Lipid solution was analyzed via reversed-phase LC-MS using an Agilent 6130 Series LC/MSD system equipped with a multi-ion source, the ChemStation software, an Agilent 1260 Infinity Series LC (Agilent Technologies), and an L-column octadecylsilyl (2.1 mm inner diameter $\times$ 150 mm; Chemicals Evaluation and Research Institute). The remaining tapes were immersed in a buffer composed of 0.1 M NaOH and 1% sodium dodecyl sulfate. Extracted soluble proteins were quantified using a BCA protein assay kit (Thermo Fisher Scientific, Waltham, MA, USA). The ratio of Cer [NP] (ng/ μ g protein) to Cer [NS] (ng/ μ g protein) was calculated.

Subjective Evaluation

Forearm itchiness was assessed by each participant using a visual analog scale (VAS) ranging from 0 to 100 mm; 0 (no itching) to 100 (maximum intensity of itching). The quality of life (QoL) was analyzed using the Japanese version of Skindex29,²⁷ which evaluates QoL in three domains (emotions, symptoms, functioning), and the average score was taken as the QoL score. Global skin condition score on the forearm was rated as follows: good, 1; slightly good, 2; cannot say which, 3; slightly bad, 4; bad, 5. dryness. Erythema score on the forearm was rated as follows: none, 0; slight, 1; weak, 2; moderate, 3; strong, 4; very strong, 5; cannot tolerate, 6.

Statistical Analysis

The eligibility of participants included in the analyses was determined based on their adherence to the study plan. The extent of change (Δ) was calculated by subtracting the values of skin properties quantified on the starting day (week 0) from the values on each measurement day. Skin measurements, VAS data, and Skindex29 data were statistically analyzed using Dunnett's multiple comparison test. Visual assessment score and subjective evaluation were analyzed using Steel's multiple comparison test. All statistical analyses were performed using BellCurve for Excel version 3.20 (Social Survey Research Information Co., Ltd., Tokyo, Japan). *p*-values less than 0.05 were considered significant.

Results

A total of 23 patients with AD were enrolled in the study. One participant was excluded from the analysis due to lack of compliance with the study protocol. Another participant could not attend the visual assessment and skin measurements at week 3. Thus, the number of participants for the evaluation was 22 at weeks 0, 1, 5, 7, and 11 and 21 at week 3.

Visual Assessment of Efficacy and Safety

At the commencement of the study (week 0), 21 of 22 participants exhibited substantial AD severity, which was classified as mild, severe, or very severe (Figure 2A). However, after one week of using the test formulations (steroid and heparinoid), a notable and significant improvement ($p < 0.01$ vs week 0) was observed in symptoms (Figure 2A). All the participants sustained significantly improved symptom states throughout the subsequent treatment ($p < 0.01$ vs week 0) and post-treatment periods ($p < 0.05$ vs week 0) (Figure 2A). Dryness, erythema, and scratch marks were significantly reduced after one-week use of the test formulations ($p < 0.01$, $p < 0.05$, $p < 0.05$, vs week 0, respectively), and remained in good condition thereafter (Figure 2B–D). No adverse events were observed during the study period.

Changes in Skin Properties Due to Measurement Device

Assessment of the skin condition at the test site revealed that skin hydration significantly increased after one-week use of the test formulations, remaining in the same state during the subsequent treatment period (Table 1). TEWL significantly decreased in week 3 and remained in the same state during the subsequent treatment and post-treatment periods (Table 1). Values related to skin color, a^* , which is an indicator for redness, did not exhibit significant changes (Δ) throughout the study period, but its value at week 7 was significantly reduced in comparison to week 1 (Table 1). Additionally, the average melanin level, which is an indicator of pigmentation, was significantly reduced at weeks 7 and 11, in comparison to week 0 (Table 1).

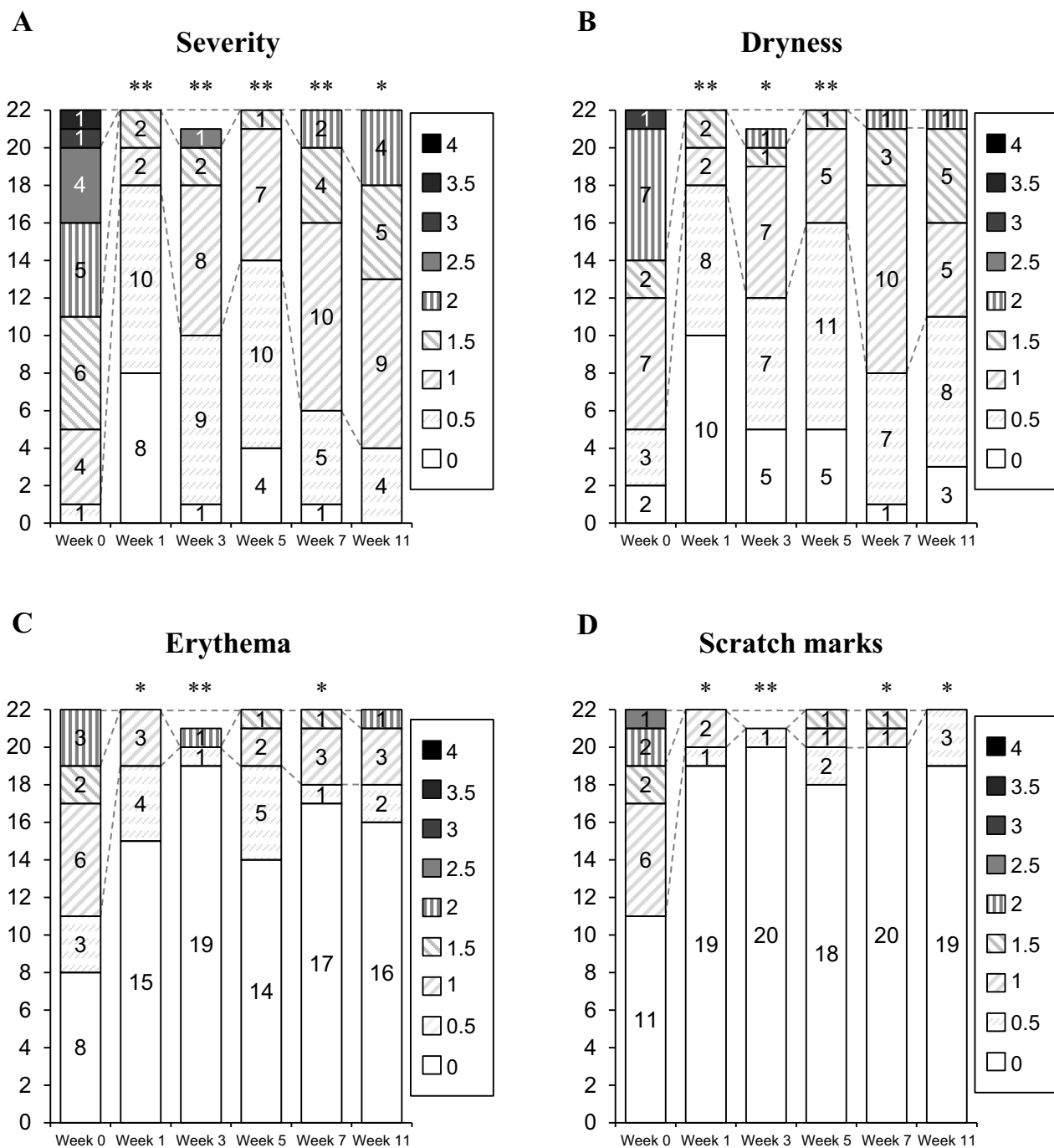


Figure 2 Visual assessment of efficacy.

Notes: The skin condition of the test site was visually scored by a dermatologist. Changes in the severity of atopic dermatitis (A). Atopic dermatitis severity was scored from 0 to 4 as follows: none, 0; slight, 0.5; mild, 1; between mild and moderate, 1.5; moderate, 2; between moderate and severe, 2.5; severe, 3; between severe and profound, 3.5; and profound, 4. Changes in dryness (B), erythema (C), and scratch marks (D) were scored from 0 to 4 as follows: none, 0; none to slight, 0.5; slight, 1; between slight and mild, 1.5; mild, 2; between mild and moderate, 2.5; moderate, 3; between moderate and severe, 3.5; and severe, 4. Statistical analysis was conducted using Steel's multiple comparison test, with week 0 as control. * $p < 0.05$, ** $p < 0.01$.

Changes in the Ratio of Ceramide Molecules in the Stratum Corneum

We analyzed the abundance ratio of NP to NS type ceramide (Cer [NP]/[NS] ratio), which is an indicator of epidermal turnover, from the SC collected by tape stripping. No significant changes were observed in the Cer [NP]/[NS] ratio throughout the study period, but the amount of change (Δ) from week 0 significantly increased after the treatment period, and was

Table 1 Instrumental Analysis of Skin and Ceramide (Cer) Analysis

Parameter	Unit		Treatment Period					Post-Treatment Period
			Week 0	Week 1	Week 3	Week 5	Week 7	Week 11
Skin color ^a	AU	Raw data	14.2 ± 1.8	13.6 ± 2.5	13.8 ± 1.9	13.9 ± 2.6	13.4 ± 2.2	13.8 ± 1.9
		Δ	0	−0.6 ± 1.1	−0.4 ± 0.8	−0.4 ± 1.3	−0.8 ± 1.2*	−0.5 ± 0.9
Average melanin level	AU	Raw data	0.57 ± 0.08	0.56 ± 0.09	0.56 ± 0.08	0.57 ± 0.08	0.56 ± 0.08	0.56 ± 0.08
		Δ	0	−0.01 ± 0.01	−0.01 ± 0.01	−0.01 ± 0.01	−0.02 ± 0.02**	−0.02 ± 0.02**
TEWL	g/m ² /h	Raw data	8.8 ± 3.7	7.7 ± 2.5	5.9 ± 1.8**	6.3 ± 1.5**	6.2 ± 1.7**	6.3 ± 1.9**
		Δ	0	−1.1 ± 3.2	−2.8 ± 3.1*	−2.5 ± 3.7*	−2.6 ± 3.6*	−2.5 ± 3.4*
Skin hydration (Conductance)	μS	Raw data	52.2 ± 40.4	156.3 ± 126.1**	114.0 ± 69.2*	128.4 ± 75.1**	121.4 ± 71.6*	73.2 ± 49.3
		Δ	0	104.1 ± 112.2**	60.9 ± 52.2*	76.2 ± 61.3**	69.2 ± 75.7**	21.0 ± 52.6
Cer[NP]/[NS] ratio	AU	Raw data	2.24 ± 0.79	-	-	-	2.53 ± 0.63	2.58 ± 0.71
		Δ	0	-	-	-	0.29 ± 0.47*	0.34 ± 0.47**

Notes: The skin conditions at the test site were assessed. The extent of change (Δ) was calculated by subtracting the skin property measurement value recorded on day 1 (week 0) from the skin property measurement value recorded on each measurement day. Values are shown as mean ± standard deviation. Statistical analysis was conducted using Dunnett's multiple comparison test, with week 0 as the control. *Redness; *p < 0.05, **p < 0.01.

Abbreviation: AU, Arbitrary units.

maintained in the post-treatment period (Table 1). The median TEWL value at week 0 was used as a basis to divide the study participants into high-TEWL (group with weak SC barrier function at the outset, n = 11) and low-TEWL groups (n = 11), and analyses were conducted on each group. The TEWL of the low TEWL group showed no significant change throughout the study period, whereas that of the high TEWL group decreased after one-week use of the test formulations, with the decrease maintained even in the subsequent treatment and post-treatment periods (Figure 3A and B). Additionally, the Cer [NP]/[NS] of the low TEWL group exhibited no significant changes throughout the study period, whereas that of the high TEWL group significantly increased (Figure 3C and D).

Changes in Subjective Assessment by the Participants

The study participants assessed the condition of the test site and their QoL. Both the itchiness VAS score and QoL assessment score significantly decreased after one-week use of the test formulations, and this decrease was maintained even in the subsequent treatment and post-treatment periods (Table 2). The study participants also evaluated the condition of the test site in terms of overall assessment, dryness, and redness. A significant improvement was observed in all the three parameters after one-week use of the test formulations (Table 3). The significantly improved state relative to that at week 0 was maintained even in the subsequent treatment period.

Discussion

The skin of patients with AD becomes dry and loses its barrier function, both in terms of water retention and allergen-entry control.^{7,13} Therefore, AD treatment requires improvement of stratum corneum function as well as the suppression of inflammation.¹⁶ Previous research evaluated the efficacy of steroid and heparinoid formulations that form a lamellar structure after application and drying for the treatment of mild to moderate AD cases, with a significant improvement in stratum corneum function compared to that achieved by formulations without a lamellar structure.^{23,24}

This study verified the efficacy of the combined use of a topical steroid drug and a moisturizer with heparinoid (both containing synthetic pseudo-ceramide that form a lamellar structure after application and drying). The combination treatment reduced the severity of dermatological findings within one week, which was maintained throughout the

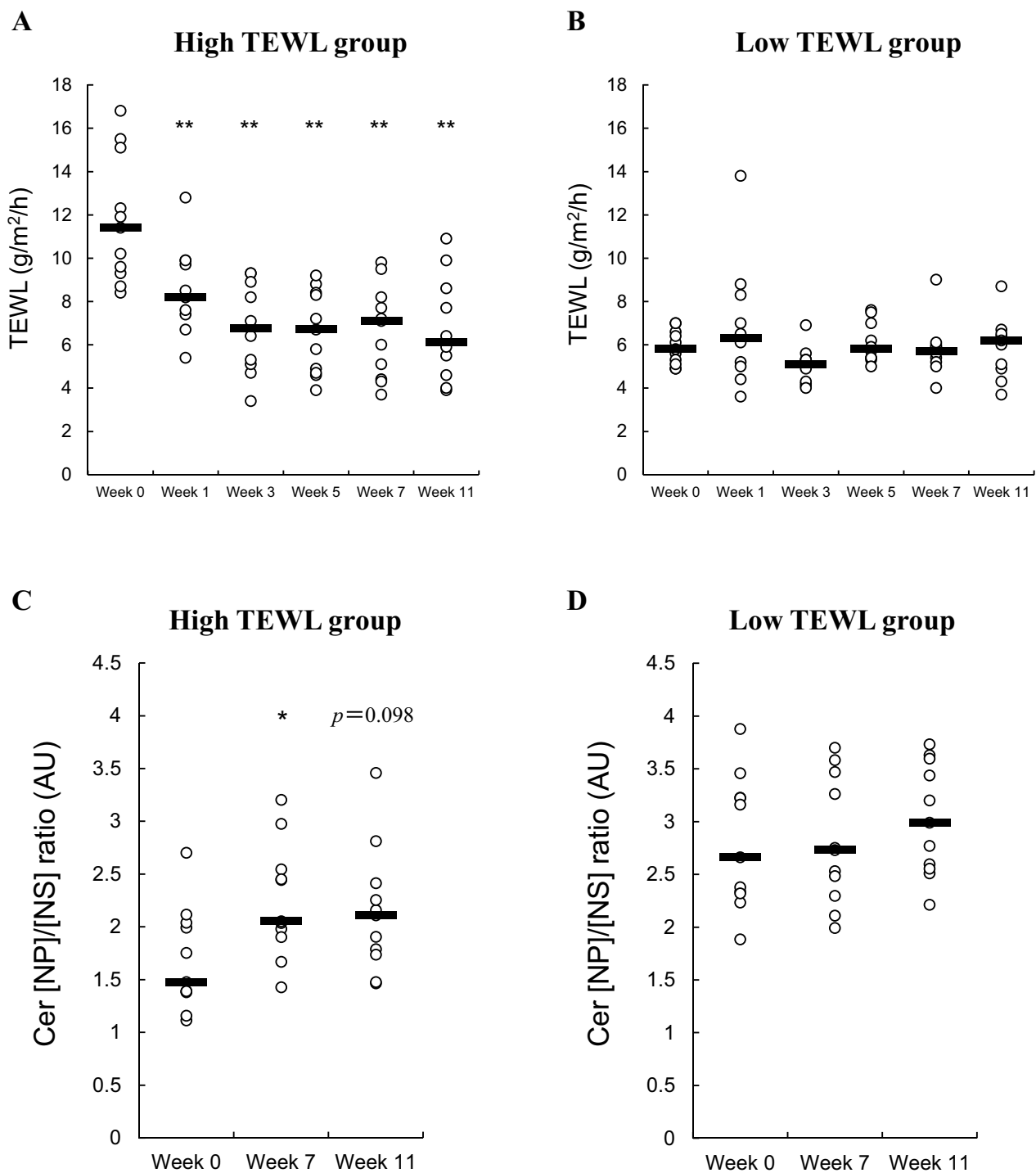


Figure 3 Cluster analysis of skin properties and epidermal turnover based on the skin types of the participants.

Notes: The median TEWL value at week 0 was used as a basis to divide the participants into high-TEWL (group with weak barrier at outset, $n = 11$) and low-TEWL groups ($n = 11$), whereafter stratification analysis was conducted. Changes in TEWL (**A** and **B**) and the ratio of ceramide molecular species in the stratum corneum (Cer [NP]/[NS]), which is an epidermal turnover indicator (**C** and **D**). Statistical analysis of TEWL results (**A** and **B**) was conducted using Steel's multiple comparison test, with week 0 as control. Statistical analysis of the Cer [NP]/[NS] results (**C** and **D**) was conducted using Dunnett's multiple comparison test, with week 0 as the control. * $p < 0.05$, ** $p < 0.01$, ○: individual participants, —: median.

Table 2 Subjective Evaluation of Skin Conditions (1)

Parameter	Unit	Treatment Period					Post-Treatment Period
		Week 0	Week 1	Week 3	Week 5	Week 7	Week 11
Itchiness (VAS)	AU	45.2 ± 24.1	19.8 ± 19.2**	16.9 ± 19.3**	18.1 ± 20.2**	19.4 ± 20.0**	24.1 ± 19.0**
QoL	AU	45.1 ± 12.1	32.9 ± 9.3**	35.8 ± 10.7*	35.6 ± 12.9*	34.6 ± 12.0*	36.2 ± 11.7*

Notes: Values are shown as the mean ± standard deviation. Statistical analysis was performed using Dunnett's multiple comparison test, with week 0 as the control. * $p < 0.05$, ** $p < 0.01$.

Abbreviation: AU, Arbitrary units.

Table 3 Subjective Evaluation of Skin Condition (2)

	Score	Treatment Period					Post-Treatment Period
		Week 0	Week 1	Week 3	Week 5	Week 7	Week 11
Global	Good	3	9	11	11	10	2
	Slightly good	5	12	5	6	9	13
	Cannot say	4	1	4	4	2	5
	Slightly bad	9	0	1	1	1	2
	Bad	1	0	0	0	0	0
	p-value	-	< 0.01	< 0.01	< 0.01	< 0.01	NS
Dryness	None	0	5	4	7	6	2
	Slight	2	8	12	10	10	4
	Weak	7	9	4	3	2	12
	Moderate	10	0	1	2	4	4
	Strong	2	0	0	0	0	0
	Very strong	1	0	0	0	0	0
	Cannot tolerate	0	0	0	0	0	0
	p-value	-	< 0.01	< 0.01	< 0.01	< 0.01	< 0.05
Redness	None	0	5	4	7	6	2
	Slight	2	8	12	10	10	4
	Weak	7	9	4	3	2	12
	Moderate	10	0	1	2	4	4
	Strong	2	0	0	0	0	0
	Very Strong	1	0	0	0	0	0
	Cannot Tolerate	0	0	0	0	0	0
	p-value	-	< 0.01	< 0.01	< 0.05	< 0.05	< 0.05

Note: Statistical analysis was conducted using Steel's multiple comparison test, with week 0 as the control.

Abbreviation: NS, Not significant.

treatment period (Figure 2A). Furthermore, no adverse events were observed, nor was significant worsening of AD symptoms noted. The QoL of the participants significantly improved within one week of the combination treatment, and this increase was maintained throughout the treatment period (Table 2). Furthermore, the combination treatment significantly improved the TEWL, skin hydration, and Cer [NP]/[NS], an indicator of epidermal turnover (Table 1). These results suggest that the use of the test formulations that form a lamellar structure after application and drying is conducive to AD treatment. Moreover, the results of the present study showed that perceived itchiness by patients and scratch marks observed by dermatologists were both significantly suppressed within one week, and these effects persisted throughout the treatment period (Table 2, Figure 2). Thus, the combined use of the test formulations improved itchiness

and continuously suppressed scratching behavior. The combined use of the test formulations also improved erythema and pigmentation (Tables 1 and 3). The beneficial effects of the combination use may include reduced inflammation achieved through suppression of the above-mentioned itchiness and scratching,² which in turn reduced pigmentation.²⁸ Improving the skin barrier function and preventing allergen entry are important for reducing itchiness in patients with AD. The reduced itchiness achieved by the test formulations (Table 2) is thought to be due to enhanced SC function. It should be noted that coatings of formulations with lamellar structure also have a physical barrier function that suppresses allergen entry.²⁴ Interestingly, the improvement in SC function in the present study was most prominent in the participants with weak barrier function at the outset (Figure 3A). These participants experienced a significant decrease in the TEWL and an improved Cer [NP]/[NS] ratio, which is an indicator of epidermal turnover (Figure 3C). These benefits could be attributed to the pseudo-ceramides contained in the formulations. Patients with AD who exhibit low TEWL have low ceramide levels;²⁹ the pseudo-ceramides are introduced between stratum corneum cells, thereby improving barrier function. Another factor contributing to these benefits could be attributed to the coating effect from the lamellar structure of the formulation. Improvements in TEWL have been reported by coating the skin.³⁰ Although the primary factor underlying the above-described beneficial effects is unclear, the present study and our previous study^{23,24} indicated the importance of base formulations in the development of topical agents. Validation with larger sample sizes and long-term randomized controlled trials will be necessary to further strengthen the evidence.

AD has a high incidence in infants, and has been proposed to cause different allergic symptoms, a phenomenon known as atopic march.⁵ Allergen protection is also important from the perspective of suppressing of atopic march. Moreover, barrier care from the neonatal period and early childhood can not only prevent the onset and exacerbation of AD but may also suppress the occurrence of various allergic diseases.^{5,17,31} Considering the benefits described herein, although our findings are limited to adults, the combined use of topical anti-inflammatory drug with a steroid and topical moisturizer with heparinoid in lamellar structure-based formulations may be particularly useful for treating AD in infants and newborns. This aspect will be worth considering in our future studies.

Conclusion

The efficacy of the combined use of a topical steroid drug and a moisturizer with heparinoid, both in lamellar structure-based formulations, was confirmed. The test formulations improved the QoL of the participants and their skin hydration and TEWL, which are important for skin barrier function during the treatment in AD patients. To treat AD, which is referred to as a barrier disease, the topical agents form a lamellar structure is suitable as topical agents, which is able to improve skin condition.

Acknowledgments

We thank the staff at the Delmalabo Co., Ltd. for their considerable cooperation during the study. We are also grateful to all the volunteers who participated in the study.

Disclosure

Yoshinori Kinugasa and Takahiro Nishizaka were employees of Kao Corporation at the time the study was conducted. Keita Okoshi, Joji Okada, and Makoto Iijima are currently affiliated with a different section within Kao Corporation. The authors have no other conflicts of interest to declare in this work.

References

1. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387(10023):1109–1122. doi:10.1016/S0140-6736(15)00149-X
2. Pavlis J, Yosipovitch G. Management of itch in atopic dermatitis. *Am J Clin Dermatol*. 2018;19(3):319–332. doi:10.1007/s40257-017-0335-4
3. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers*. 2018;4(1):1. doi:10.1038/s41572-018-0001-z
4. Imokawa G. Autocrine and paracrine regulation of melanocytes in human skin and in pigmentary disorders. *Pigment Cell Res*. 2004;17(2):96–110. doi:10.1111/j.1600-0749.2003.00126.x
5. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. *Allergy*. 2014;69(1):17–27. doi:10.1111/all.12268
6. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol*. 2008;121(6):1337–1343. doi:10.1016/j.jaci.2008.01.022

7. Catherine MacK Correa M, Nebus J. Management of patients with atopic dermatitis: the role of emollient therapy. *Dermatol Res Pract*. 2012;2012:836931. doi:10.1155/2012/836931
8. Lampe MA, Burlingame AL, Whitney J, et al. Human stratum corneum lipids: characterization and regional variations. *J Lipid Res*. 1983;24(2):120–130. doi:10.1016/S0022-2275(20)38005-6
9. Imokawa G, Hattori M. A possible function of structural lipids in the water-holding properties of the stratum corneum. *J Invest Dermatol*. 1985;84(4):282–284. doi:10.1111/1523-1747.ep12265365
10. Tagami H, Kobayashi H, O'goshi K, Kikuchi K. Atopic xerosis: employment of noninvasive biophysical instrumentation for the functional analyses of the mildly abnormal stratum corneum and for the efficacy assessment of skin care products. *J Cosmet Dermatol*. 2006;5(2):140–149. doi:10.1111/j.1473-2165.2006.00241.x
11. Matsumoto M, Umemoto N, Sugiura H, Uehara M. Difference in ceramide composition between 'dry' and 'normal' skin in patients with atopic dermatitis. *Acta Derm Venereol*. 1999;79(3):246–247. doi:10.1080/000155599750011183
12. Yokose U, Ishikawa J, Morokuma Y, et al. The ceramide [NP]/[NS] ratio in the stratum corneum is a potential marker for skin properties and epidermal differentiation. *BMC Dermatol*. 2020;20(1):6. doi:10.1186/s12895-020-00102-1
13. Hata M, Tokura Y, Takigawa M, et al. Assessment of epidermal barrier function by photoacoustic spectrometry in relation to its importance in the pathogenesis of atopic dermatitis. *Lab Invest*. 2002;82(11):1451–1461. doi:10.1097/01.LAB.0000036874.83540.2B
14. Katayama I, Aihara M, Ohya Y, et al. Japanese guidelines for atopic dermatitis 2017. *Allergol Int*. 2017;66(2):230–247. doi:10.1016/j.alit.2016.12.003
15. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol*. 2018;120(1):10–22.e2. doi:10.1016/j.anai.2017.10.039
16. Elias PM, Wakefield JS, Man MQ. Moisturizers versus current and next-generation barrier repair therapy for the management of atopic dermatitis. *Skin Pharmacol Physiol*. 2019;32(1):1–7. doi:10.1159/000493641
17. Hon KL, Leung AKC, Barankin B. Barrier repair therapy in atopic dermatitis: an overview. *Am J Clin Dermatol*. 2013;14(5):389–399. doi:10.1007/s40257-013-0033-9
18. Seghers AC, Cai SC, Ho MS, et al. Evaluation of a pseudoceramide moisturizer in patients with mild-to-moderate atopic dermatitis. *Dermatol Ther*. 2014;4(1):83–92. doi:10.1007/s13555-014-0048-z
19. Matsuki H, Kiyokane K, Matsuki T, Sato S, Imokawa G. Reevaluation of the importance of barrier dysfunction in the nonlesional dry skin of atopic dermatitis patients through the use of two barrier creams. *Exog Dermatol*. 2004;3(6):293–302. doi:10.1159/000091910
20. Hata M, Tokura Y, Takigawa M, et al. Efficacy of using pseudoceramide-containing cream for the treatment of atopic dry skin in comparison with urea cream. *Nishinohon J Dermatol*. 2002;64(5):606–611. doi:10.2336/nishinohonhifu.64.606
21. Ishikawa J, Shimotoyodome Y, Chen S, et al. Eucalyptus increases ceramide levels in keratinocytes and improves stratum corneum function. *Int J Cosmet Sci*. 2012;34(1):17–22. doi:10.1111/j.1468-2494.2011.00675.x
22. Imokawa G, Ishida K. Role of ceramide in the barrier function of the stratum corneum, implications for the pathogenesis of atopic dermatitis. *J Clin Exp Dermatol Res*. 2014;5(01):1–12. doi:10.4172/2155-9554.1000206
23. Okoshi K, Kinugasa Y, Ito S, et al. Efficacy of pseudo-ceramide-containing steroid lamellar cream in patients with mild to moderate atopic dermatitis: a Randomized, double-blind study. *Dermatol Ther*. 2022;12(8):1823–1834. doi:10.1007/s13555-022-00766-2
24. Matsuoka M, Okoshi K, Ito S, et al. Efficacy of heparinoid cream containing pseudo-ceramide for remission of atopic dermatitis. *Clin Cosmet Invest Dermatol*. 2021;14:1839–1847. doi:10.2147/CCID.S337930
25. Saeki H, Furue M, Furukawa F, et al. Guidelines for management of atopic dermatitis. *J Dermatol*. 2009;36(10):563–577. doi:10.1111/j.1346-8138.2009.00706.x
26. Fukagawa S, Haramizu S, Sasaoka S, Yasuda Y, Tsujimura H, Murase T. Coffee polyphenols extracted from green coffee beans improve skin properties and microcirculatory function. *Biosci Biotechnol Biochem*. 2017;81(9):1814–1822. doi:10.1080/09168451.2017.1345614
27. Fukuhara S. *Measuring HRQOL of Patients with Skin Disease. Manual of DLQI and Skindex29 Japanese Version*. Tokyo: Shorinsha; 2004.
28. Costin GE, Hearing VJ. Human skin pigmentation: melanocytes modulate skin color in response to stress. *FASEB J*. 2008;21(4):976–994. doi:10.1096/fj.06-6649rev
29. Ishikawa J, Narita H, Kondo N, et al. Changes in the ceramide profile of atopic dermatitis patients. *J Invest Dermatol*. 2010;130(10):2511–2514. doi:10.1038/jid.2010.161
30. Grubauer G, Elias PM, Feingold KR. Transepidermal water loss: the signal for recovery of barrier structure and function. *J Lipid Res*. 1989;30(3):323–333. doi:10.1016/S0022-2275(20)38361-9
31. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):824–830.e6. doi:10.1016/j.jaci.2014.07.060

Clinical, Cosmetic and Investigational Dermatology

Dovepress

Publish your work in this journal

Clinical, Cosmetic and Investigational Dermatology is an international, peer-reviewed, open access, online journal that focuses on the latest clinical and experimental research in all aspects of skin disease and cosmetic interventions. This journal is indexed on CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/clinical-cosmetic-and-investigational-dermatology-journal>