Hindawi
Dermatologic Therapy
Volume 2023, Article ID 4811165, 8 pages
https://doi.org/10.1155/2023/4811165

Research Article

Side-by-Side Comparative Study of a Moisturizer and Topical Tacrolimus for Treating Mild to Moderate Atopic Dermatitis: A Randomized Single-Blinded Clinical Trial

Joonho Shim,[1] **Yeon Joo Jung**,[1] **Se Jin Oh**,[1] **Jong Hee Lee**,[1,2] **and Jihye Park**[1]

[1]*Department of Dermatology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[2]*Department of Medical Device Management & Research, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, Republic of Korea*

Correspondence should be addressed to Jihye Park; jh1204.park@samsung.com

Received 22 December 2022; Revised 20 February 2023; Accepted 4 April 2023; Published 17 April 2023

Academic Editor: Francesco Lacarrubba

The appropriate use of therapeutic moisturizers could reduce the need for more aggressive treatment in the management of atopic dermatitis (AD). We conducted a randomized, side-by-side, single-blinded, comparative study in 41 mild to moderate AD patients to compare a moisturizer and topical tacrolimus for restoring skin barrier function and managing AD. A moisturizer was applied twice daily for 4 weeks to one side of the flexural areas (moisturizer group). Topical tacrolimus was applied on the other side of the tested area (tacrolimus group). Biophysical skin parameters were measured at baseline, week 2, and week 4. Clinical qualitative assessments were also conducted. Analysis of the trend from baseline to week 4 revealed that the hydration level was significantly increased in both groups ($p < 0.01$, respectively). No biophysical parameters were significantly different between the two groups. Differences in the modified Eczema Area and Severity Index scores between the baseline and week 4 were significantly higher in the tacrolimus group than those in the moisturizer group ($p = 0.002$). In the Investigator's Global Assessment, a significantly larger proportion of patients in the tacrolimus group showed clinical improvement than that in the moisturizer group at week 4 ($p = 0.027$). Although topical tacrolimus was superior to the moisturizer in preventing the clinical exacerbation of AD, the moisturizer was not inferior to topical tacrolimus in restoring skin barrier function. Therefore, moisturizer is considered to play an essential role in maintenance therapy for AD. Physicians need to emphasize the benefits of moisturizers when educating their patients.

1. Introduction

Atopic dermatitis (AD) is one of the most prevalent chronic inflammatory skin diseases. It usually develops in childhood and may persist into adulthood [1]. AD is usually characterized by recurrent eczematous lesions with intense itching, leading to excoriations, lichenification, and susceptibility to cutaneous infections [2]. Skin barrier dysfunction plays a critical role in the development of AD [3, 4]. Alterations in the skin barrier can lead to the increased penetration of environmental allergens and infective organisms that can cause persistent inflammation [5].

The daily application of moisturizer has been proposed to restore the skin barrier and constitutes the mainstay of treatment for AD regardless of its severity [6, 7]. Data from randomized controlled trials (RCTs) showed that moisturizers had long- and short-term steroid-sparing effects in treating mild to moderate AD [8–10]. Moisturizers could restore a defective skin barrier while decreasing exposure to irritants and exerting anti-inflammatory and antimicrobial effects [9, 11, 12].

Several RCTs have compared topical corticosteroids and moisturizers in the management of AD [13]. However, to the best of our knowledge, no studies have compared moisturizers and topical tacrolimus. Tacrolimus is a topical calcineurin inhibitor, an anti-inflammatory, and steroid-sparing agent, shown to be efficacious for the acute flares and in maintenance therapy of AD [14]. Many guidelines

recommend the use of topical tacrolimus for both the active and proactive treatment of AD [14]. Proactive therapy with topical tacrolimus could reduce the frequency of relapses [15–17].

Therefore, the aim of this study was to compare the effectiveness of a moisturizer with topical tacrolimus for restoring skin barrier function and managing AD.

2. Patients and Methods

2.1. Trial Design. This study was a single-center, randomized, investigator-blinded, and side-by-side a comparative clinical trial designed to determine the effectiveness of a moisturizer and topical tacrolimus for treating mild to moderate AD. This study was conducted at the outpatient dermatology clinics at the Samsung Medical Center (SMC), Seoul, Republic of Korea between January 2021 and June 2022. The study protocol was approved by the Institutional Review Board (IRB) of SMC (IRB No. SMC 2020-08-148) and registered with the World Health Organization Clinical Research Information Service (https://cris.nih.go.kr/cris, KCT0007962). All patients provided written informed consent before the commencement of the study.

2.2. Study Participants. Eligible patients were 20–70 years of age who met the clinical criteria for AD as defined by Hanifin and Rajka [18] and had Eczema Area and Severity Index (EASI) scores of ≤7 (mild) or 7–21 (moderate) [19]. To be eligible for this side-by-side comparative study, all patients had to have symmetrically distributed lesions on the flexural areas, such as the antecubital area or popliteal fossa. Atopic dermatitis (AD) was diagnosed by a board-certified dermatologist. The exclusion criteria included the following: active states of other dermatitis or eczematous conditions, skin infection requiring oral or topical antimicrobial therapy, or previous treatment with oral or topical corticosteroids or immunosuppressants within the past four weeks.

2.3. Materials. The test cream used in this study was BARRIEDERM LOTION MD® (Cell Fusion C, Seoul, Republic of Korea), which contained various components, including a lipid mixture (Neo-CMS® formula) enriched by ceramide NP and fatty acids (FAs) of diverse chain lengths. Ceramide NP was synthesized by combining FAs of various lengths (C16–C24) derived from four plant oils (moringa oil, meadowfoam seed oil, macadamia oil, and shea butter oil) and phytosphingosine from yeast (*Pichia ciferrii*) fermentation [20–22]. The major components of the study cream are listed in Table S1.

2.4. Treatment. In this side-by-side comparative study, patients were randomly assigned to apply moisturizer either on their right or left side and topical tacrolimus on the other side. They were instructed by the dermatologist to apply the moisturizer twice daily to one side of the flexural areas, such as the antecubital area or popliteal fossa (moisturizer group), for 4 weeks. On the opposite side of the tested area, the patients applied moisturizer in the morning and 0.1% topical tacrolimus (Protopic®, Fujisawa Healthcare, Inc. Deerfield, IL, USA) in the evening to serve as a control (tacrolimus group). There were a total of three visits: week 0 (baseline), week 2, and week 4. At each visit, the patients underwent clinical examinations and biophysical skin parameter measurements with pictures taken of the tested areas. No other moisturizers were allowed on the antecubital or popliteal fossa during the study period. The amount of the study cream used was assessed by recording the weight of the returned containers at the end of the study period. Patients were allowed to discontinue trial participation for any reason at any time.

2.5. Clinical Assessment of AD Severity. AD disease's severity was assessed using the Investigator's Global Assessment (IGA) and the modified Eczema Area and Severity Index (mEASI). The IGA scores represent the evaluation of clinical improvements at week 2 and week 4 compared to the baseline (week 0). Three blinded dermatologists evaluated the digital photographs using the following criteria: (1) much worse; (2) worse; (3) no change; (4) improved; and (5) much improved. The mEASI evaluations were measured out of the tested areas only and were measured by the same dermatologists. The mEASI was defined as the sum of erythema, induration/papulation, excoriation, and lichenification. The average degree of the severity of each sign was assigned a score from 0 to 3, where 0 was none, 1 was mild, 2 was moderate, and 3 was severe.

2.6. Biophysical Skin Parameters. All biophysical skin parameter evaluations, including hydration, transepidermal water loss (TEWL), erythema index (EI), and melanin index (MI), were performed by a single technician at baseline, week 2, and week 4. During the measurements, relative humidity was controlled at $50 \pm 5\%$ and the room temperature was maintained at $21 \pm 1^{\circ}C$. Measurements were made at the antecubital area or popliteal fossa, to which the moisturizer or topical tacrolimus had been applied. Three repetitive measurements were taken for each site, and the mean value was used for the analyses. The participants were instructed not to use the test moisturizer or topical tacrolimus on the day of the visit to minimize any problems during measurements. Skin hydration and TEWL were measured using a DermaLab Combo® (Cortex Technology, Hasund, Denmark). The MI and EI were measured using a DSM III Colormeter® (Cortex Technology).

2.7. Sample Size Estimation and Statistical Analysis. A sample size of 37 patients and 37 sites in each arm was sufficient to detect a clinically important difference of 2.5 between groups in improving TEWL, assuming a standard deviation of 5.24 using a paired *t*-test with 80% power and a two-sided 0.05 significance level. Adjusting for a possible drop-out rate of 15%, 43 patients per group were considered necessary.

Statistical analyses were executed using SAS, version 9.4 (SAS Institute Inc, Cary, NC, USA), and statistical software

R, version 4.0.3. (R Foundation for Statistical Computing, Vienna, Austria). The continuous data are expressed as the mean ± standard deviation (SD). The examined parameters of mEASI, hydration, TEWL, MI, and EI were tested for normal distribution, using the Shapiro–Wilk test. The Wilcoxon signed-rank sum test was used to compare the biophysical skin parameters and mEASI scores in each treatment group before and after treatment. McNemar's Chi-square test was used to compare the IGA scores. The statistical significance was considered for p values of less than 0.05. The α-level was adjusted according to Bonferroni's modification to account for multiple testing issues.

3. Results

3.1. Patient Population. A total of 43 patients with mild to moderate AD were recruited. Two of the enrolled patients dropped out during the study period due to COVID-19 infection and loss of follow-up. The remaining 41 patients completed the treatment protocol and all follow-up visits. The study flow diagram is shown in Figure 1. The demographic and other baseline characteristics of the patients are described in Table 1. The patients had a mean (±SD) age of 31.8 (±10.0) years. They were predominantly females (56.1%, $n = 23$). The mean (±SD) EASI scores at baseline were 10.4 (±7.3). There were no significant differences in mEASI scores and biophysical skin parameters between the moisturizer and tacrolimus groups at baseline.

3.2. Clinical Assessments. The mean mEASI scores were significantly decreased at week 2 compared to baseline in both groups ($p < 0.0001$, respectively) (Figures 2 and 3(a)). Significant improvements in mEASI scores were sustained through 4 weeks of treatment in both groups (Figure 3(a)). The mEASI scores were not significantly different between the two treatment sides at week 2. However, mEASI scores were significantly different between the two groups at week 4 ($p < 0.01$).

The proportion of patients who showed clinical improvements according to IGA scores was not significantly different between the two groups at week 2 (Figure 4(a)). However, at week 4, significantly more patients showed clinical improvements in the tacrolimus group versus the moisturizer group ($p = 0.027$, Figure 4(b)). The IGA exacerbation was not observed in the tacrolimus group at week 4, whereas it was reported in 8 patients (19.5%) in the moisturizer group.

3.3. Biophysical Skin Parameters. At baseline, no skin biophysical parameter in either group showed a statistically significant difference (Figure 3). Skin hydration levels were significantly increased at week 4 compared to baseline in the moisturizer and the tacrolimus groups ($p < 0.001$ and $p < 0.01$, respectively) (Figure 3(b)). At week 4, the TEWL and MI values were decreased in both groups (Figures 3(c) and 3(d)). The EI scores were increased in the tacrolimus group but decreased in the moisturizer group (Figure 3(e)). However, none of these changes were statistically significant. There were no significant differences in biophysical skin parameters between the two groups at baseline, week 2, or week 4.

4. Discussion

In this study, the IGA and mEASI scores, as well as the biophysical parameters, were assessed to objectively compare a moisturizer with topical tacrolimus. The analysis of the trend from baseline to week 4 revealed a decrease in TEWL and the degree of hyperpigmentation in both groups. The increase in erythema in the tacrolimus group is presumed to have been due to skin irritation after using topical tacrolimus. The most common adverse events after the application of topical tacrolimus are skin burning, including a burning sensation, pain, erythema, and flushes [23]. On the other side, to which moisturizer was applied, the degree of erythema was decreased compared to the tacrolimus group. Only skin hydration levels were significantly increased in the moisturizer group compared to the tacrolimus group. The mEASI scores were significantly decreased in both groups. There was no significant difference between the tacrolimus group and the moisturizer group in biophysical skin parameters, but there was a difference in the mEASI scores between the two groups. Both groups showed similar patterns of change over time in other biophysical skin parameters except erythema, suggesting similar effects in maintaining skin barrier function in both groups. However, the results of visual assessments (mEASI and IGA) showed more clinical improvements in the tacrolimus group than in the moisturizer group at week 4, indicating that it is difficult to prevent the worsening of AD symptoms due to various environmental stimuli with moisturizer alone.

The IGA scores at week 4 showed no exacerbation in the tacrolimus group. However, 8 patients (19.5%) in the moisturizer group showed exacerbations after moisturizer application. The etiology of AD is multifactorial, with interactions between genetics, immune, and environmental factors [24]. Numerous environmental injuries to the skin occurring throughout life may trigger or exacerbate AD [25]. Proactive topical tacrolimus therapy has been shown to be effective in reducing the number of flares [26, 27]. Unlike a topical tacrolimus, our data suggest that AD patients could experience acute flares with only moisturizer treatment without using anti-inflammatory agents.

As dry skin is an important disease feature of AD, skin moisturization may constitute an integral part of standard treatment [28]. Previous studies revealed that moisturizers could hydrate the skin and alleviate the epidermal barrier dysfunction in AD [29, 30]. A previous meta-analysis study on childhood AD compared the effectiveness of moisturizers and topical corticosteroids, and the authors concluded that topical corticosteroids were more effective than moisturizers/vehicles [13]. According to two studies comparing moisturizers and topical pimecrolimus, moisturizers were as effective as topical pimecrolimus in improving AD [31, 32]. However, no comparative study has been conducted on topical tacrolimus. Moreover, unlike corticosteroids, topical tacrolimus and moisturizers are used as maintenance

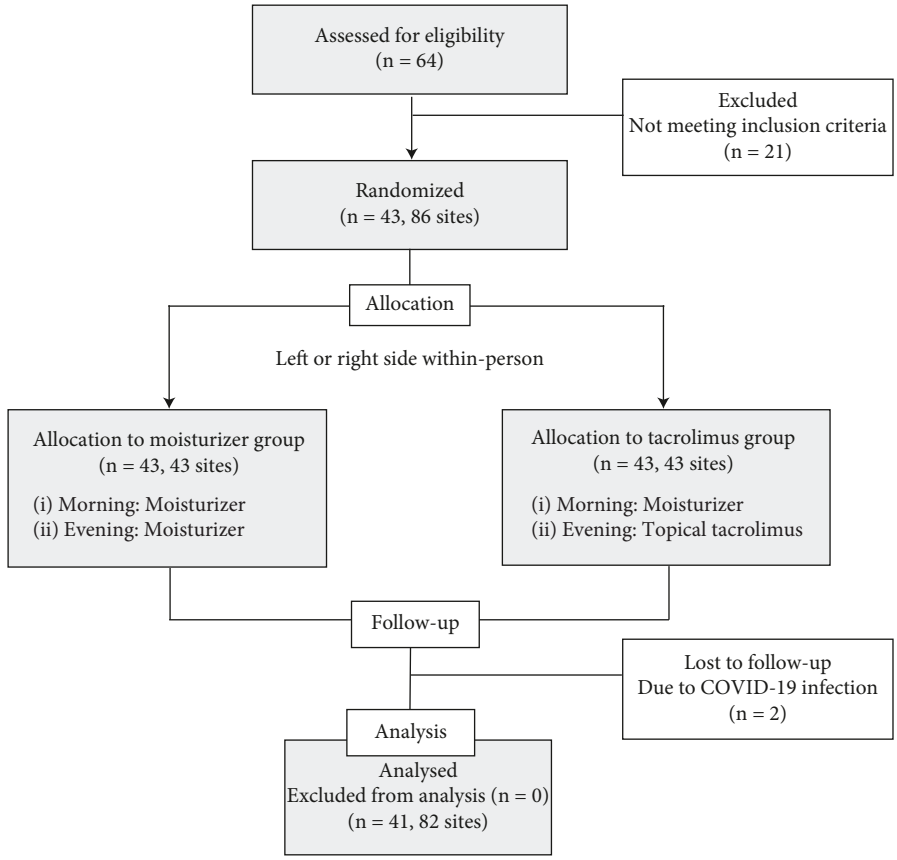

Figure 1: Flowchart diagram of the side-by-side, single-blinded, and randomized clinical trial.

Table 1: Demographic and baseline characteristics of patients.

$N = 41$ (82 sites)			
Age (yr)			
Mean ± SD		31.8 ± 10.0	
Median (range)		28 (20–56)	
Sex			
Male, *n* (%)		18 (43.9%)	
Female, *n* (%)		23 (56.1%)	
EASI			
Mean ± SD		10.4 ± 7.4	
Median (range)		9 (0.9–26.0)	
	Moisturizer group (41 sites)	Topical tacrolimus group (41 sites)	*p* value
mEASI			
Mean ± SD	7.5 ± 3.3	7.4 ± 3.3	0.906
TEWL			
Mean ± SD	27.2 ± 17.7	27.8 ± 16.4	0.534
Hydration			
Mean ± SD	131.6 ± 86.7	135.2 ± 102.1	0.688
MI			
Mean ± SD	41.2 ± 6.4	40.8 ± 6.0	0.336
EI			
Mean ± SD	14.3 ± 3.3	14.4 ± 3.3	0.911

therapies for AD. Thus, we sought to compare the effects of a moisturizer with topical tacrolimus.

Ceramides are composed of sphingoid bases linked with various types of FAs, and they are an essential constituent of stratum corneum (SC) intercellular lipids [33]. Reduced levels of ceramides have been associated with several skin diseases such as AD [34]. Ceramide NP, also known as ceramide 3, consists of a phytosphingosine

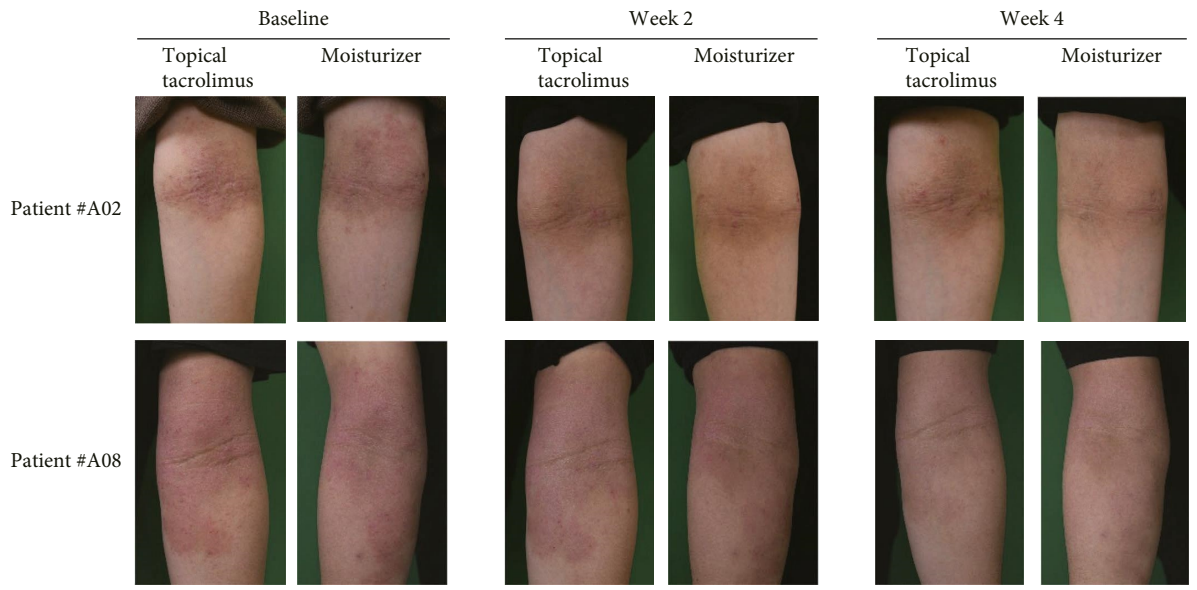

Figure 2: Clinical pictures of representative patients before and after 4 weeks of treatment with moisturizers and topical tacrolimus.

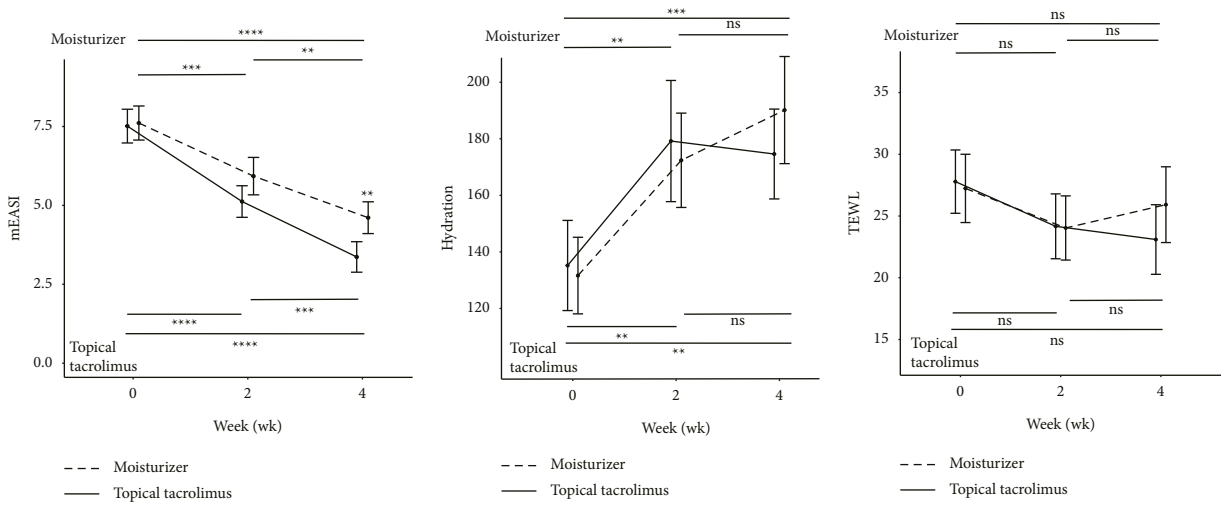

Figure 3: Continued.

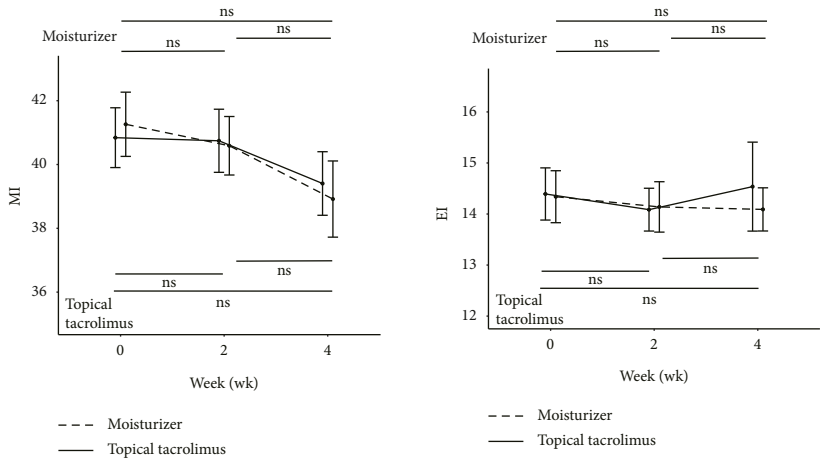

Figure 3: Mean values of (a) mEASI, (b) hydration, (c) TEWL, (d) MI, and (e) EI throughout the follow-up visits (mean ± standard error). (a) Differences in mEASI scores between the moisturizer and tacrolimus groups were significantly greater at week 4 than that at baseline. (b) Hydration levels were significantly increased at week 2 and week 4 compared to baseline in both groups. (c, d At week 4, TEWL and MI values were decreased in both the moisturizer and tacrolimus groups although they were not statistically significant. (e) At week 4, EI scores were increased in the tacrolimus group but decreased in the moisturizer group, although these increases or decreases were not statistically significant. mEASI, modified Eczema Area and Severity Index; TEWL, transepidermal water loss; MI, melanin index; EI, erythema index, ns; not significant. $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$.

Moisturizer / Tacrolimus	Worse	No change	Improved	Much improved	Total
Worse	0	1	0	0	1
No change	3	12	1	0	16
Improved	3	7	10	0	20
Much improved	0	0	3	1	4
Total	6	20	14	1	41

p-value = 0.0741

(a)

Moisturizer / Tacrolimus	Worse	No change	Improved	Much improved	Total
Worse	0	0	0	0	0
No change	2	9	1	0	12
Improved	4	5	8	1	18
Much improved	2	0	6	3	11
Total	8	14	15	4	41

p-value = 0.0271

(b)

Figure 4: Proportions of IGA scores at (a) week 2 and (b) week 4. At week 4, the proportion of patients in the tacrolimus group who showed clinical improvements was statistically higher than that in the moisturizer group. IGA, Investigator's Global Assessment.

base in an amide linkage with nonhydroxy acids [35, 36]. Most previous research study on skin barrier recovery has been conducted on a particular ceramide with a single-chain FA. However, interest in diverse chain lengths has increased recently [37, 38]. The use of a lipid mixture enriched with ceramide NP and FAs of diverse chain lengths improved the recovery rate of the damaged SC and enhanced skin hydration better than a single C18-ceramide NP [37, 38].

This study had several limitations. First, we did not compare the test moisturizer to other moisturizers. Thus, we were unable to conclude that it was superior to others. Second, blinding of the intervention was not possible for the study participants. Thus, we could not evaluate the patient satisfaction with the treatments.

To the best of our knowledge, this was the first trial to compare the efficacies of a moisturizer with topical tacrolimus for treating mild to moderate AD. The findings of this

study suggest that a moisturizer could provide beneficial effects on mild to moderate AD. Thus, healthcare providers should encourage patients with AD to regularly apply moisturizers to restore skin barrier function.

Data Availability

The data that support the findings of this study are included in this article and are available from the corresponding author upon request.

Ethical Approval

This study was approved by the Institutional Review Board of Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea (SMC 2020-08-148).

Consent

An informed consent was acquired from all subjects prior to enrollment. The subjects in the figures provided written informed consent for the publication of their case details.

Disclosure

The CMS LAB had no role in the data collection, data analysis, data interpretation, manuscript preparation, manuscript review, or manuscript approval.

Conflicts of Interest

The authors declare that they have no conflicts of interests.

Authors' Contributions

J. P. and J. H. L. participated in the conception and design of the trial protocol. Analysis and interpretation of the data were supported by J. S., Y. J. J., S. J. O., and J. P., J. S. and Y. J. J. prepared the figures and/or tables. J. S. and Y. J. J. drafted the manuscript. J. H. L., S. J. O., and J. P. conducted a critical review of the manuscript. All authors gave final approval of the version for publication.

Acknowledgments

This study was funded by the CMS LAB (Seoul, Korea).

Supplementary Materials

Supplementary Table 1. Components of the test moisturizer. (*Supplementary Materials*)

References

[1] S. Ständer, "Atopic dermatitis," *New England Journal of Medicine*, vol. 384, no. 12, pp. 1136–1143, 2021.

[2] E. Galli, B. Cinicola, R. Carello et al., "Atopic dermatitis," *Acta BioMedica: Atenei Parmensis*, vol. 91, no. 11, Article ID e2020011, 2020.

[3] K. Kabashima, "New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity," *Journal of Dermatological Science*, vol. 70, no. 1, pp. 3–11, 2013.

[4] B. E. Kim and D. Y. M. Leung, "Significance of skin barrier dysfunction in atopic dermatitis," *Allergy, Asthma & Immunology Research*, vol. 10, no. 3, pp. 207–215, 2018.

[5] Y. C. Giam, A. A. Hebert, M. V. Dizon et al., "A review on the role of moisturizers for atopic dermatitis," *Asia Pacific Allergy*, vol. 6, no. 2, pp. 120–128, 2016.

[6] Y. Valdman-Grinshpoun, D. Ben-Amitai, and A. Zvulunov, "Barrier-restoring therapies in atopic dermatitis: current approaches and future perspectives," *Dermatology Research and Practice*, vol. 2012, Article ID 923134, 6 pages, 2012.

[7] E. J. van Zuuren, Z. Fedorowicz, R. Christensen, A. Lavrijsen, and B. W. M. Arents, "Emollients and moisturisers for eczema," *Cochrane Database of Systematic Reviews*, vol. 2, no. 2, Article ID Cd012119, 2017.

[8] F. Boralevi, M. Saint Aroman, A. Delarue et al., "Long-term emollient therapy improves xerosis in children with atopic dermatitis," *Journal of the European Academy of Dermatology and Venereology*, vol. 28, no. 11, pp. 1456–1462, 2014.

[9] R. Grimalt, V. Mengeaud, and F. Cambazard, "The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study," *Dermatology*, vol. 214, no. 1, pp. 61–67, 2007.

[10] A. W. Lucky, A. D. Leach, P. Laskarzewski, and H. Wenck, "Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children," *Pediatric Dermatology*, vol. 14, no. 4, pp. 321–324, 1997.

[11] J. M. Peltonen, L. Pylkkänen, C. T. Jansén et al., "Three randomised phase I/IIa trials of 5% cis-urocanic acid emulsion cream in healthy adult subjects and in patients with atopic dermatitis," *Acta Dermato-Venereologica*, vol. 94, no. 4, pp. 415–420, 2014.

[12] W. P. Tan, S. Suresh, H. L. Tey, L. Y. Chiam, and A. T. Goon, "A randomized double-blind controlled trial to compare a triclosan-containing emollient with vehicle for the treatment of atopic dermatitis," *Clinical and Experimental Dermatology*, vol. 35, no. 4, pp. e109–e112, 2010.

[13] A. B. Fishbein, K. Mueller, J. Lor, P. Smith, A. S. Paller, and A. Kaat, "Systematic review and meta-analysis comparing topical corticosteroids with vehicle/moisturizer in childhood atopic dermatitis," *Journal of Pediatric Nursing*, vol. 47, pp. 36–43, 2019.

[14] P. Calzavara-Pinton, G. Fabbrocini, G. Girolomoni et al., "Topical tacrolimus in adult atopic dermatitis: a consensus based on a 15-year experience," *Giornale italiano di dermatologia e venereologia: Organo ufficiale Societa italiana di dermatologia e sifilografia*, vol. 155, no. 1, pp. 8–13, 2020.

[15] L. F. Eichenfield, W. L. Tom, T. G. Berger et al., "Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies," *Journal of the American Academy of Dermatology*, vol. 71, no. 1, pp. 116–132, 2014.

[16] D. Rubel, T. Thirumoorthy, R. W. Soebaryo et al., "Consensus guidelines for the management of atopic dermatitis: an Asia-Pacific perspective," *The Journal of Dermatology*, vol. 40, no. 3, pp. 160–171, 2013.

[17] J. Ring, A. Alomar, T. Bieber et al., "Guidelines for treatment of atopic eczema (atopic dermatitis) part I," *Journal of the European Academy of Dermatology and Venereology*, vol. 26, no. 8, pp. 1045–1060, 2012.

[18] J. M. HanifIn and G. Rajka, "Diagnostic features of atopic dermatitis," *Acta Dermato-Venereologica*, vol. 60, pp. 44–47, 1980.

[19] Y. A. Leshem, T. Hajar, J. M. Hanifin, and E. L. Simpson, "What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study," *British Journal of Dermatology*, vol. 172, no. 5, pp. 1353–1357, 2015.

[20] H. G. Maister, S. P. Rogovin, F. H. Stodola, and L. J. Wickerham, "Formation of extracellular sphingolipids by microorganisms: IV. Pilot-plant production of tetraacetylphytosphingosine by hansenula ciferrii," *Applied Microbiology*, vol. 10, no. 5, pp. 401–406, 1962.

[21] D. Börgel, M. van den Berg, T. Hüller et al., "Metabolic engineering of the non-conventional yeast Pichia ciferrii for production of rare sphingoid bases," *Metabolic Engineering*, vol. 14, no. 4, pp. 412–426, 2012.

[22] Y. Barenholz, N. Gadot, E. Valk, and S. Gatt, "Identification of the enzymatic lesions responsible for the accumulation of acetylated sphingosine bases in the yeast Hansenula ciferri," *Biochimica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism*, vol. 306, no. 2, pp. 341–345, 1973.

[23] A. Baldo, M. Cafiero, P. Di Caterino, and L. Di Costanzo, "Tacrolimus ointment in the management of atopic dermatitis," *Clinical, Cosmetic and Investigational Dermatology*, vol. 2, pp. 1–7, 2009.

[24] I. A. Deckers, S. McLean, S. Linssen, M. Mommers, C. P. van Schayck, and A. Sheikh, "Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies," *PLoS One*, vol. 7, no. 7, Article ID e39803, 2012.

[25] R. Kantor and J. I. Silverberg, "Environmental risk factors and their role in the management of atopic dermatitis," *Expert Review of Clinical Immunology*, vol. 13, no. 1, pp. 15–26, 2017.

[26] A. Wollenberg, S. Reitamo, F. Atzori et al., "Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment," *Allergy*, vol. 63, no. 6, pp. 742–750, 2008.

[27] D. Thaçi, S. Reitamo, M. A. Gonzalez Ensenat et al., "Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study," *British Journal of Dermatology*, vol. 159, no. 6, pp. 1348–1356, 2008.

[28] T. Bieber, "Atopic dermatitis," *New England Journal of Medicine*, vol. 358, no. 14, pp. 1483–1494, 2008.

[29] S. G. Danby, K. Brown, T. Higgs-Bayliss, J. Chittock, L. Albenali, and M. J. Cork, "The effect of an emollient containing urea, ceramide NP, and lactate on skin barrier structure and function in older people with dry skin," *Skin Pharmacology and Physiology*, vol. 29, no. 3, pp. 135–147, 2016.

[30] M. Breternitz, D. Kowatzki, M. Langenauer, P. Elsner, and J. W. Fluhr, "Placebo-controlled, double-blind, randomized, prospective study of a glycerol-based emollient on eczematous skin in atopic dermatitis: biophysical and clinical evaluation," *Skin Pharmacology and Physiology*, vol. 21, no. 1, pp. 39–45, 2008.

[31] J. J. Emer, A. Frankel, A. Sohn, and M. Lebwohl, "A bilateral comparison study of pimecrolimus cream 1% and a topical medical device cream in the treatment of patients with atopic dermatitis," *Journal of Drugs in Dermatology*, vol. 10, no. 7, pp. 735–743, 2011.

[32] A. Frankel, A. Sohn, R. V. Patel, and M. Lebwohl, "Bilateral comparison study of pimecrolimus cream 1% and a ceramide-hyaluronic acid emollient foam in the treatment of patients with atopic dermatitis," *Journal of Drugs in Dermatology: Journal of Drugs in Dermatology*, vol. 10, no. 6, pp. 666–672, 2011.

[33] W. M. Holleran, Y. Takagi, and Y. Uchida, "Epidermal sphingolipids: metabolism, function, and roles in skin disorders," *FEBS Letters*, vol. 580, no. 23, pp. 5456–5466, 2006.

[34] B. Skolová, B. Janůšová, J. Zbytovská et al., "Ceramides in the skin lipid membranes: length matters," *Langmuir*, vol. 29, no. 50, pp. 15624–15633, 2013.

[35] C. L. Fischer, K. S. Walters, D. R. Drake et al., "Sphingoid bases are taken up by *Escherichia coli* and *Staphylococcus aureus* and induce ultrastructural damage," *Skin Pharmacology and Physiology*, vol. 26, no. 1, pp. 36–44, 2013.

[36] T. Pavicic, U. Wollenweber, M. Farwick, and H. C. Korting, "Anti-microbial and -inflammatory activity and efficacy of phytosphingosine: an in vitro and in vivo study addressing acne vulgaris," *International Journal of Cosmetic Science*, vol. 29, no. 3, pp. 181–190, 2007.

[37] S. H. Lim, E. J. Kim, C. H. Lee et al., "A lipid mixture enriched by ceramide NP with fatty acids of diverse chain lengths contributes to restore the skin barrier function impaired by topical corticosteroid," *Skin Pharmacology and Physiology*, vol. 35, no. 2, pp. 112–123, 2022.

[38] M. J. Oh, Y. H. Cho, S. Y. Cha et al., "Novel phytoceramides containing fatty acids of diverse chain lengths are better than a single C18-ceramide *N*-stearoyl phytosphingosine to improve the physiological properties of human stratum corneum," *Clinical, Cosmetic and Investigational Dermatology*, vol. 10, pp. 363–371, 2017.