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ORIGINAL ARTICLE

Treatment of atopic dermatitis with KAM-3008, a barrier-based, non-steroidal topical cream

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Abstract

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with cutaneous hyper-reactivity to environmental triggers, and is characterized by pruritic eczematous skin lesions. Recent insights into the pathophysiology of AD point to the important role that abnormal barrier permeability plays, which leads to compromised hydration, common micro-organismal colonization and immune dysregulation. Current treatment strategies for AD, such as topical corticosteroids and moisturizers, control the disease symptom's severity and duration. KAM-3008 is a novel, barrier-based, steroid-free, topical cream indicated for the relief of symptoms associated with AD. In addition to moisturizing and emollient ingredients, several herbal extracts have been incorporated into the formulation to enhance its anti-allergic and anti-inflammatory properties. *Methods*: In this study, the safety and efficacy of KAM-3008 body cream in relieving the symptoms of AD in adult subjects after 7, 14 and 21 days of treatment were investigated using the transepidermal water loss (TEWL), skin hydration and scoring atopic dermatitis (SCORAD) measurements. *Results and conclusions*: Based on both the quantitative TEWL and qualitative SCORAD assessments, we found that KAM-3008 body cream is a safe, well-tolerated and efficacious stand-alone treatment for the relief of AD symptoms.

Keywords

Anti-allergic, anti-oxidant, atopic dermatitis, eczema, herbal extracts, SCORAD, transepidermal water loss

History

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Introduction

Atopic dermatitis (AD) is a pruritic, inflammatory disease which significantly reduces the patients' quality of life (1). AD usually starts in early infancy with a lifetime prevalence of 10–20% in children and 1–3% in adults (2). The disease is characterized by eczematous lesions, xerosis and lichenification, as well as subjective symptoms, such as pruritus and insomnia. In severe cases, fluid-filled blisters develop in affected areas.

Defects in the epidermal permeability barrier are thought to be one of the major etiological risks for the development of AD (3–5). This hypothesis is supported by the direct correlation between abnormal permeability barrier function and the disease severity (6–8). The barrier abnormality is characterized by genetic loss-of-function mutations in *FLG*, which encodes an S100 fused-type structural protein involved in epithelial differentiation (9). In addition, barrier abnormality is also characterized by distinctive lipid aberrations, including a global reduction in the three key stratum corneum (SC) lipids (e.g. cholesterol, free fatty acids and ceramides) known to mediate epidermal permeability barrier function (10). Moreover, the impaired barrier facilitates sustained allergen penetration, thereby provoking downstream immunological characteristic features of AD, including eosinophil infiltration, increased serum IgE levels and activation of mast cells and DCs via high-affinity Fc receptors (11,12). Imbalance in adaptive and innate immunity contributes to reduced epidermal differentiation which damages the skin barrier's integrity. Additional etiological factors, such as genetic predisposition and environmental factors, affect AD pathogenesis.

The treatment of AD is generally based on a multi-stage approach (13). First-line treatments include: (a) a reduction, if possible, in exposure to triggering factors, including allergens, irritants, temperature changes, emotional stress, etc.; (b) intermittent application of topical corticosteroids and (c) regular application of emollients and moisturizers to preserve and restore the integrity of the skin's barrier functions. In some cases, management of the disease may also include one or more of the following: topical calcineurin inhibitors, antibiotics, antihistamines, phototherapy and oral administration of corticosteroids. In severe and chronic cases, eczema is treated by suppressing the immune system by methotrexate, cyclosporin or azathioprine. Unfortunately, due to their side effects, corticosteroids or immune-suppressive agents are not recommended for long-term use, especially in children (14,15).

Kamedis KAM-3008 body cream is a barrier-based, steroid free, topical cream. In addition to its moisturizing and emollient ingredients, several herbal extracts have been added to the formulation. Four main ingredients of the cream are from herbal sources: *Rheum palmatum* root extract, *Scutellaria baicalensis* root extract, *Cnidium monnieri* fruit extract and Dipotassium

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Glycyrrhizate, a saponin produced from licorice root (*Glycyrrhiza glabra*). These herbal components are known for their anti-oxidant, anti-allergic and anti-inflammatory activities (16,17). *Rheum palmatum* and *Scutellaria baicalensis* root extracts and their active ingredients emodin and baiclain, respectively, have demonstrated strong anti-oxidative (18) and anti-inflammatory (19–21) activities in a variety of *in vitro* and *in vivo* studies. Glycyrrhizin, the water-soluble constituent of licorice, has also been shown to exhibit strong anti-inflammatory activities (22–24). *Cnidium monnieri* fruit extract and its active components were found to significantly inhibit allergic responses (25) and pruritic behaviors in mice models (26).

The cream was specifically developed for the relief of symptoms associated with AD. Additional ingredients, such as cholesterol, ceramides and fatty acid, have been added to revitalize the skin barrier. The cream is supplemented with moisturizing components, such as glycerin, shea butter, hyaluronic acid and allantoin. Moreover, the cream does not contain any parabens or perfumes that can be harmful to individuals with atopic and sensitive skin; it adheres to the injured tissue and eliminates contaminating factors related to dermatitis, thereby protecting the skin from further irritation. Similarly, the cream helps to maintain a moist skin environment, thus facilitating the healing process of the impaired skin barrier function.

Here, we report the results of an open label, self-controlled, interventional, efficacy/safety study evaluating the effect of Kamedis KAM-3008 body cream on symptoms of mild to severe AD in adult patients.

Methods

Study objectives

The primary objective of the study was to assess the efficacy of KAM-3008 cream in relieving the symptoms of AD after 7, 14 and 21 days of treatment with the goal of achieving at least 25% reduction of the AD severity at the end of the 21-day period. Secondary objectives included the ability of KAM-3008 to maintain a moist skin environment measured with transepidermal water loss (TEWL) and hydration tests, as well as the safety of the tested cream assessed by the number and severity of cream-related adverse events (AEs).

Study population

Subjects participating in the current study were male and female adults 18 years of age or older, diagnosed with AD according to Hanifin's and Rajka's criteria (27). All the subjects consented to apply only the test product twice a day (morning and evening) for a period of three consecutive weeks and to return for follow-up and final visits according to the study schedule. Main exclusion criteria included the presence of another dermatological disease/condition that could interfere with clinical evaluation, previous history of allergy to cosmetic products or to any ingredients of the test formulation, use of topical or systemic immune-modulating agents or steroids within two weeks of the screening visit, phototherapy within four weeks of the screening visit, expected extensive sun exposure for the duration of the study, use of any experimental treatment within two weeks from the screening visit and pregnancy or lactation.

Study design

The study was carried out as an open-labeled, self-controlled trial. Subjects were enrolled at one site (Dermatest, Münster, Germany) and the study was conducted in full conformance with ''clinical-dermatological studies referring to GCP – optimized to the cosmetic industries'' (ISO 9001:2008 TÜV Rheinland, Germany). Participation was voluntary and subjects signed an informed consent form prior to participation.

Study assessments

Baseline, follow-up and final visit measurements of AD severity via the scoring atopic dermatitis (SCORAD) scale, AD characteristics (including individual intensity symptoms, extent and subjective symptoms), TEWL and skin hydration were evaluated.

The SCORAD scale (28,29) consists of three scoring components: extent (A, maximal contribution: ~20%), intensity (B, maximal contribution: ~60%) and subjective symptoms (C, maximal contribution: ~20%). The SCORAD values were calculated according to the equation: $A/5 + 7B/2 + C$ (29). Skin moisture levels were evaluated using the TEWL test, in which evaporation was measured using an evaporimeter (DermaLab TransEpidermal Water Loss Module, Cortex Technology, Hadsund, Denmark). Hydration levels were measured using a corneometer (CM825 from Courage & Khazaka, Cologne, Germany).

Statistical analysis

Data were reported as means with standard deviations. Statistical analyses were carried out using multivariate analysis of variance (MANOVA), *t*-test and chi-square. Significance levels were $p < 0.05$ (significant, *in figures and table) and $p < 0.001$ (highly significant, **in figures and table) or not significant (NS in figures and table). All statistical calculations were computed with Excel and associated QI macros.

Results

Demographic and baseline characteristics

Twenty subjects (15 females and 5 males) were recruited for the study. The average age was 45 ± 13 years (range: 19–67; median: 47). At baseline, the average SCORAD was 41.3 ± 12 (range: 21.5–60.6; median: 39.95); there were no SCORAD differences between males and females (unpaired *t*-test: $p = 0.46$) and there was no correlation between age and SCORAD ($R = -0.08$, $p = 0.76$).

Efficacy

Primary endpoint

An overall steady improvement, starting from 7 days after the beginning of treatment and reaching at least 25% in the SCORAD score after 21 days, was observed in 16 out of 20 subjects. A 7% deterioration in the SCORAD was observed in one patient at the first follow-up visit, which later improved during subsequent visits to 29%. An unchanged SCORAD score throughout the study was observed in one subject. MANOVA analysis demonstrates a significant time effect ($p < 0.001$, $n = 20$) on the mean values of SCORAD. When compared to the baseline scores, mean SCORAD remained static for 7 days ($p = 0.18$), but improved by $18 \pm 12\%$ ($p < 0.001$) and $31 \pm 15\%$ ($p < 0.001$), after 14 and 21 days, respectively. Of the three components of SCORAD (extent, intensity and subjective symptoms) extent remained stable throughout the study (MANOVA, NS), while intensity and subjective symptoms showed significant improvement. Figure 1 depicts the effect of treatment on the severity of AD as measured with SCORAD.

Since this study evaluated the effect of treatment on existing symptoms, only subjects who expressed each of the symptoms at baseline were included in this part of the analysis. Improvement in dryness, lichenification, excoriation and oozing became apparent from day 14 onwards, reaching statistical significance (chi-square) on day 21, whereas a significant improvement in

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erythema was observed from day 14 onwards. There was a similar trend regarding edema, however the difference in means was not statistically significant. Table 1 illustrates the effect of KAM-3008 treatment on each of the six individual intensity symptoms.

The percentage of subjects with moderate-to-severe intensity symptoms dramatically decreased after 21 days of treatment, as shown in Figure 2. Prominent effects were observed for moderate-to-severe erythema and dryness, appearing in 90% and 95% of the subjects at the baseline, and improving to 25% and 40% of the subjects, respectively, after 21 days of treatment. Figure 3 illustrates the effect of treatment on pruritus and insomnia. When compared to baseline, pruritus steadily decreased over time (one-way MANOVA: $p<0.001$). Changes relative to baseline at 7, 14 and 21 days were: $-15\pm22\%$ ($p<0.01$), $-29\pm23\%$ ($p<0.001$) and $-48\pm18\%$ ($p<0.001$), respectively. For insomnia the changes were not statistically significant. Notably, throughout the study, none of the patients required additional medication or any type of rescue therapy.

Secondary endpoints

Figure 4 depicts the effect of KAM-3008 on TEWL and skin hydration at baseline and after 21 days. There was a significant reduction in TEWL/evaporation ($-14\pm7\%$, $p<0.001$) coupled with a significant increase in hydration ($29\pm7\%$, $p<0.001$) on the treated skin, whereas on the control untreated sites no changes were observed in either measurement. With regards to safety, no AEs were reported throughout the study.

Discussion

For decades, topical corticosteroids have been the treatment of choice for the inflammation, pruritus and erythema associated with AD. However, chronic use or even short-term use of high potency preparations was found to be associated with adverse effects, including skin atrophy, striae (30), and in rare cases, inhibition of the HPA axis (31). Another potential drawback of topical corticosteroids is rebound flaring, i.e. the skin improves when corticosteroids are used and when the treatment is terminated there is a severe recurrence of symptoms. Chronic use of topical corticosteroids can also induce disruption of the skin barrier, which is counterproductive in patients with atopic conditions, causing great concern for both patients and healthcare providers alike. Calcineurin inhibitors, originally used to prevent organ graft rejection, have been approved for topical intermittent use in AD patients. Nevertheless, these inhibitors are not effective in all patients and their use may be associated with stinging or burning sensations in a subset of patients. The current treatment landscape demonstrates a major need for novel, corticosteroids-free treatments for AD with minimal local side effects.

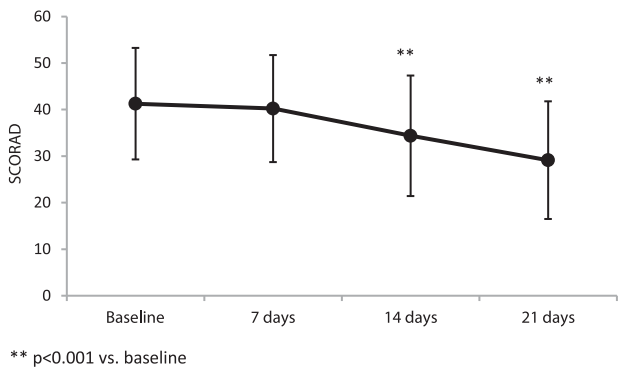


Figure 1. Time course of AD severity as measured by SCORAD (mean ± SD).

In this study, the safety and efficacy of KAM-3008 body cream in providing relief for symptoms of AD were demonstrated using both quantitative and qualitative measurements. The primary expected outcome measure was a 25% reduction in the severity of AD symptoms after 21 days of treatment. This was achieved by using the cream twice daily, which decreased severity of the symptoms by 31%. The constant increase in SCORAD improvement throughout the study suggests that longer use of KAM-3008 can result in even greater symptomatic relief.

From the patient's point of view, pruritus is one of the most disturbing symptoms of dermatitis and has a profound effect on the quality of life through sleeplessness and anxiety (32). Itching reduction is a major treatment goal to prevent further injury of skin with an impaired barrier. The positive effect of KAM-3008 treatment on pruritus was observed from day 7 onwards and increased to a mean improvement of 48% reported by subjects on day 21. In contrast, changes in insomnia were not statistically significant, probably due to the small population suffering from this symptom ($n=9$).

Secondary objectives were also achieved. The study demonstrated the ability of KAM-3008 to prevent water loss and to enhance skin hydration. The safety of the tested product was markedly demonstrated, with no AEs occurring throughout the study. Most importantly, no secondary infections (indicating worsening of AD) developed during the trial in any of the subjects, including the five subjects with severe AD (SCORAD > 50), who had a higher risk for complications.

Application of KAM-3008 provides a mechanical barrier, and maintains a moist skin environment. These combined therapeutic activities protect the skin from additional irritation, and facilitate the healing process. The addition of several herbal extracts known for their anti-oxidative and anti-pruritus activities (16,17,26) to our product protects the skin from oxidative stress and mechanical

Table 1. Effect of treatment on individual intensity symptoms: analysis of means.

		Baseline	7 days		14 days		21 days	
Intensity symptom	*n*	Mean ± SD (%)	Mean ± SD (%)	Chi-square (*p*)	Mean ± SD (%)	Chi-square (*p*)	Mean ± SD (%)	Chi-square (*p*)
Dryness	20	2.2 ± 0.5	2.2 ± 0.5	NS	1.9 ± 0.6	NS	1.5 ± 0.6	**
Erythema	20	2.0 ± 0.5	2.0 ± 0.5	NS	1.7 ± 0.7	*	1.3 ± 0.6	**
Edema	11	1.6 ± 0.5	1.6 ± 0.5	NS	1.2 ± 0.6	NS	1.2 ± 0.6	NS
Lichenification	20	1.6 ± 0.6	1.5 ± 0.6	NS	1.3 ± 0.7	NS	1.1 ± 0.6	**
Excoriation	20	1.5 ± 0.5	1.4 ± 0.5	NS	1.1 ± 0.6	NS	1.1 ± 0.4	**
Oozing	18	1.3 ± 0.5	1.3 ± 0.5	NS	1.1 ± 0.6	NS	0.8 ± 0.6	**

For each intensity symptom, only subjects who expressed the symptom at baseline were analyzed.
*$p<0.01$ versus baseline.
**$p<0.001$ versus baseline.

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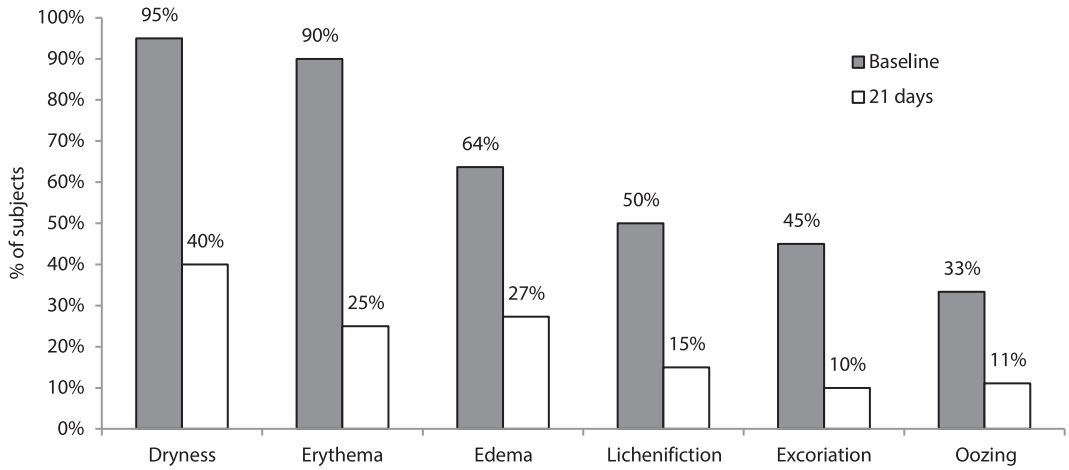


Figure 2. Percent of subjects with moderate-to-severe score of AD symptoms.

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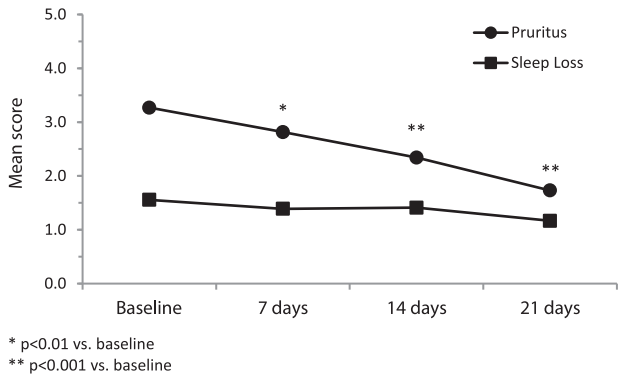


Figure 3. Effect of treatment on individual subjective symptoms.

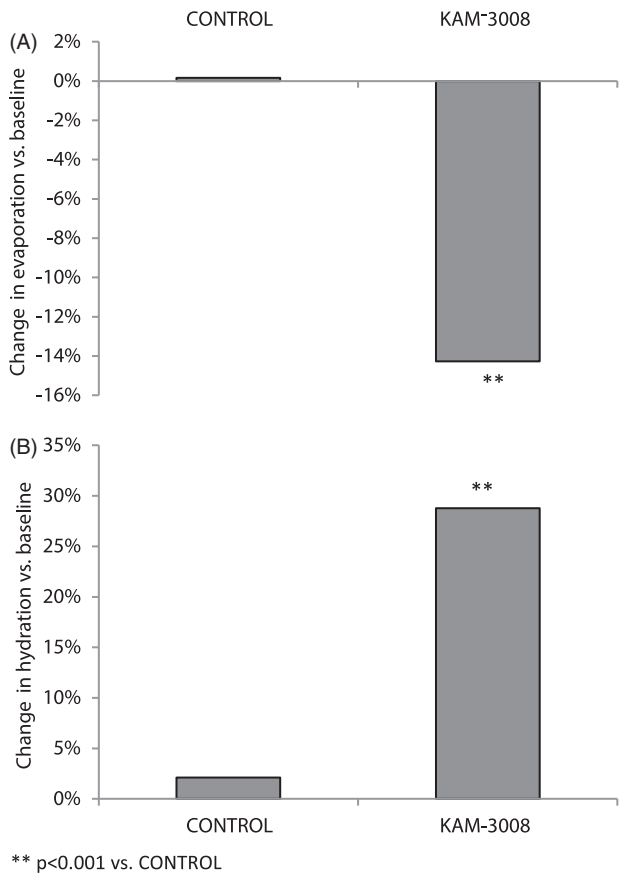


Figure 4. Effect of treatment on moisturizing level of the skin. For each subject, ''KAM-3008'' represents an average of three samples from the affected and treated areas; ''Control'' represents an average of three samples from the non-affected areas. (A) Mean change of TEWL after 21 days, compared to baseline. (B) Mean change of hydration after 21 days, compared to baseline.

skin damage, thus further contributing to the restoration of the intact skin barrier.

Additional non-steroidal, moisturizing preparations, such as MAS063DP (33) (Atopiclair, Sinclair Pharmaceuticals, Godalming, UK) and EpiCeram (34) (Ceragenix Corp., Denver, CO) have also been tested for the treatment of AD. EpiCream is a mixture of free fatty acids, cholesterol and a synthetic ceramide. Atopiclair has a similar base with additional substances, such as shea butter and certain plant extracts. Large randomized clinical trials demonstrated the efficacy of these preparations in reducing symptoms in patients suffering from moderate to severe AD. In the Atopiclair studies, the subjects were asked to apply the cream three times daily whereas in our study, similar reductions in symptoms were seen with only twice daily applications. Besides using less medication, an additional advantage of using the cream twice daily as opposed to three times is that there is no need of taking the medication during the day when the patient is usually not at home; this pattern of application should significantly improve compliance. An additional advantage seen in the KAM-3008 study was that there were no adverse effects reported in the study in the treatment arm. In the trials of the other two creams, mild to moderate AEs were reported in the treatment arms of those trials, such as a stinging or burning sensations. In one of the trials, almost 10% of the subjects had to discontinue use of the test cream whereas in our study, no AEs were observed in the treatment arm. This could be due to the smaller sample size in our trial or that the unique composition of KAM-3008 greatly reduces such AEs and therefore can be tolerated by a wider segment of people suffering from AD.

Conclusions

In summary, the results of this study indicate that the formulation of KAM-3008 significantly reduces the intensity of the majority of AD symptoms. The treatment was safe and well-tolerated

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without any need for additional medication. Further controlled studies are being planned to confirm the results of this study and to determine more precise treatment regimens with KAM-3008. Based on both preliminary quantitative and qualitative clinical data, it was concluded that KAM-3008 body cream is a safe and effective treatment for relief of AD symptoms.

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Declaration of interest

This manuscript describes a company-sponsored study (Kamedis Ltd., Tel Aviv, Israel). Both authors are employed by Kamedis, however neither author was directly involved in the execution of the clinical study described herein.

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