ABSTRACT

Introduction: To evaluate the efficacy and safety of a pseudoceramide-containing moisturizer as maintenance therapy in patients with mild-to-moderate atopic dermatitis (AD).

Methods: This was a prospective, single-arm, open-label clinical trial of a twice-daily application of a pseudoceramide-containing moisturizer for 4 weeks as maintenance therapy in 40 patients with stable, mild-to-moderate AD in a tropical climate. Clinical and skin barrier assessment was done at week 0, week 2 and week 4. Any adverse effects were also recorded during the study period.

Results: The objective scoring atopic dermatitis decreased from 29.1 [interquartile range (IQR) 21.9–33.7] at week 0 to 22.0 (IQR 21.2–27.8) at week 4 (p < 0.001). There was no detectable difference in transepidermal water loss after 4 weeks; however, stratum corneum (SC) hydration was significantly increased from 39.7 (IQR 35.3–46.4) at week 0 to 49.2 (IQR 41.2–54.6) after 4 weeks (p < 0.001). Both Dermatology Life Quality Index and patient-oriented eczema measure showed significant improvement at week 4 (p < 0.001). The moisturizer was well tolerated with no serious adverse events recorded.

Conclusion: After 4 weeks of barrier maintenance therapy with a pseudoceramide moisturizer, there was a significant improvement in disease severity, SC hydration and quality of life in both pediatric and adult patients with mild-to-moderate AD.

Keywords: Atopic dermatitis; Ceramides; Dermatology; Pseudoceramide moisturizer; Skin barrier; Objective scoring atopic dermatitis (SCORAD); Stratum corneum hydration; Transepidermal water loss
INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease causing impaired quality of life. AD affects about 10–30% of children and 2–10% of adults [1–4]. Skin barrier dysfunction plays a critical role in the initiation, perpetuation and exacerbation of AD and the key players for a normal epidermal barrier function include lipids and proteins in the stratum corneum. Ceramides are the major constituent (50%) of these lipids [5] and have been shown to have a high water-holding capacity [6]. Patients with AD have been shown to have lower levels of ceramides, particularly type 1 and 3 [7, 8]. More recent studies have shown that in addition to the reduction of ceramides in AD skin, an increased level of short-chain ceramides can lead to an aberrant lipid organization and decreased skin barrier function in AD patients [9, 10]. Hence, a therapeutic approach to repair the skin barrier defect in AD is to normalize the amount of ceramides in the skin. The use of ceramide containing topical creams has been shown to be beneficial in the management of AD [11–13]. However, additional research is needed to determine the optimal formulary compositions.

Ceramides can be extracted from natural animal sources, but this process is lengthy and expensive with limited availability. Furthermore, there are concerns about the toxicity and the risk of transmissible infections, such as bovine spongiform encephalopathy, from bovine-derived sources [14]. Hence, synthetic pseudoceramides, which have been developed and used successfully in skin barrier repair therapy [15, 16], have a good safety profile and are less expensive than natural ceramides [5, 14].

The primary objective of this study was to demonstrate the safety and efficacy of the use of a pseudoceramide-containing moisturizer in both adults and children with mild-to-moderate AD as maintenance therapy in a tropical climate. Secondary aims were to evaluate skin physiological measurements and also the patients’ acceptability and adherence to the moisturizer.

METHODS

This was a prospective, 4-week, non-controlled open-label clinical trial to determine the safety and efficacy of a twice-daily application of a pseudoceramide moisturizer for the maintenance therapy of mild-to-moderate AD in both children and adults.

The test product in this study was Curel® Moisture cream (Kao Corporation, Tokyo, Japan), which contained 8% of a synthetic pseudoceramide, sphingolipid E (cetylpropyleneglycolhydroxyethylpalmitamide), which is analogous to endogenous ceramide type 2. It also contained Eucalyptus globules extract that has been shown to increase endogenous production of ceramides by keratinocytes [17]. The full ingredients of the study cream are listed in Table 1. Earlier animal safety studies have shown that it is non-toxic [18–20].

Study Subjects

Forty subjects were recruited from the outpatient dermatology clinics at the National Skin Centre, Singapore. Inclusion criteria included an unequivocal diagnosis of AD based on the UK Working Party's Group criteria [21], age between 7–60 years old, with stable, mild-to-moderate AD as defined by objective SCORing Atopic Dermatitis (SCORAD) scores of <15 for mild AD, and
15–40 for moderate AD [22–24]. Exclusion criteria were a recent disease flare or the use of any systemic therapy, including antibiotics, phototherapy, corticosteroids or immunosuppressants, within the past 4 weeks.

**Study Design**

There were a total of three study visits, namely, week 0, week 2 and week 4. At each visit, study subjects underwent clinical examination (including evaluation of any adverse events), skin physiological measurements and completed questionnaires related to quality of life, adverse events and their use of the study cream. The study was conducted in Singapore, which has a tropical climate with no seasonal variation. All subjects were instructed to use the study cream at least twice a day for 4 weeks on all affected areas as well as other body areas, including the forearms and cubital fossae. Subjects were allowed to use their standard medicated creams as needed, in event of a disease flare. No other moisturizers were allowed during the study period and all subjects were provided with a standardized soap-free cleanser for bathing. The use of topical corticosteroids was documented, and the amount of the study cream used was assessed by recording the weight of the returned containers at the end of the study period.

**Clinical Assessment of AD Severity**

Disease severity of AD was assessed using the objective and total SCORAD index and the three-item-severity (TIS) scores (maximum TIS score 9) [22–24]. Each case was evaluated by the same dermatologist to minimize inter-observer variability.

**Skin Physiological Studies**

Standardized measurements of stratum corneum (SC) hydration and transepidermal water loss (TEWL) were performed by a single technician. Testing was performed at a fixed
point, defined as 3 cm distal from the cubital crease over the flexor aspect of both forearms. Measurements were taken in triplicate for each site, the mean value being used for analysis. There was a washout period of 3 days prior to baseline measurements (visit 1), and subjects were instructed not to use any topical products on both forearms.

SC hydration was measured using a Corneometer® CM 825 (Courage & Khazaka GmbH, Cologne, Germany) and expressed in arbitrary units between 0 and 130. A value $\geq 50$ from the arms was interpreted as sufficiently moisturized, 35–50 as dry and $< 35$ as very dry [25, 26]. TEWL was obtained using a Tewameter® TM 300 (Courage & Khazaka GmbH, Cologne, Germany) and recorded as g/m²/h. All measurements were performed in the same room with a controlled temperature of 25 °C, after a 15-min acclimatization.

Patient’s Assessment of AD severity

Subjective scores included the Dermatology Life Quality Index (DLQI) (maximum DLQI score 30) [27, 28] and the patient-oriented eczema measure (POEM) (maximum POEM score 28) [29, 30]. Both the adult or pediatric versions of the DLQI and POEM were used accordingly. In addition, subjective scores for both pruritus and insomnia (scale from 0 to 10) were analyzed during the study period. The subject’s evaluation of the study cream was also assessed at the end of the study.

Statistical Analysis

Changes in disease severity scores, skin physiological measurements and patient subjective severity scores were analyzed at week 0, week 2 and week 4. Intention-to-treat analysis was performed. Given that these measurements were not normally distributed, the median and interquartile range (IQR) was used as descriptive statistics and overall improvements were analyzed using Friedman test. When there was significant overall improvement, post hoc pairwise comparison between weeks was conducted using the Wilcoxon signed-rank test with Bonferroni correction to test the median for paired results. The data were analyzed using SPSS® version 21 (SPSS Inc., Chicago, IL, USA). Differences were considered significant at $p < 0.05$.

RESULTS

Subject Characteristics

A total of 40 subjects with mild-to-moderate AD were recruited. There were 26 adults and 14 children (Table 2). The majority were male (75%, $n = 30$) and Chinese (92.5%, $n = 37$), with a median age of 20.5 years (range 7–37). The overall median objective SCORAD at baseline was 29.1 (IQR 21.9–33.7).

Clinical Assessment of AD severity

There was an improvement in the SCORAD and TIS scores at week 2 and week 4. At week 2, the objective SCORAD decreased to 25.1 (IQR 19.3–29.2) and at week 4, there was a further decrease to 22.0 (IQR 21.2–27.8) (Fig. 1). The median total SCORAD showed a similar reduction during the study period (Table 3).
Both overall reduction of objective SCORAD and total SCORAD were statistically significant \((p < 0.001)\). The mean TIS score also decreased over 4 weeks from a baseline score of 3 (IQR 3–5) to 2 points (IQR 1–3) at week 4 \((p < 0.001)\) (Table 3).

### Skin Physiological Measurements

SC hydration improved in 29 (85%) of the study subjects. The median of skin hydration at baseline was 39.7 (IQR 35.3–46.4) and increased to 49.2 (IQR 41.2–54.6) at week 4 \((p < 0.001)\) (Table 3).

Paradoxically, the median TEWL increased from 9.4 at baseline to 11.2 at week 4 \((p = 0.1)\) (Table 3).

### Patient Subjective symptoms

There was improvement in DLQI from a median baseline score of 6.5 (IQR 3–11) to 3 (IQR 2–7) at week 4 \((p < 0.001)\) (Table 3). The POEM showed a similar improvement: from 13 (IQR 2–7) at baseline to 6.5 (IQR 2–7) at week 4 \((p < 0.001)\) (Table 3). The pruritus score was reduced from 6 (IQR 5–7) to 4 (IQR 2–6) over the study period \((p < 0.001)\). A noticeable but not statistically significant improvement was seen in the insomnia score: from 2 (IQR 0–6) points on the visual analogue scale (VAS) scale to 0 (IQR 0–3) points at week 4 \((p = 0.03)\).

### Adverse Events

At week 2, five (12.5%) subjects reported pruritus and one (2.5%) patient reported
Table 3 Clinical assessment scores, skin physiological measurements and patient subjective scores at baseline (day 0), after 2 weeks and after 4 weeks of treatment with a pseudoceramide-containing moisturizer

|                      | Baseline n = 40 | After 2 weeks n = 40 | After 4 weeks n = 40 | p (for changes between week 0 and 4) |
|----------------------|-----------------|----------------------|----------------------|-----------------------------------|
| **Clinical assessment** |                 |                      |                      |                                   |
| Median Objective SCORAD (IQR) | 29.1 (21.9–33.7) | 25.1 (19.3–29.2)   | 22.0 (21.2–27.8)     | <0.001                           |
| Median Total SCORAD (IQR)     | 38.8 (28.6–43.8) | 29.7 (21.4–38.8)   | 28.1 (21.5–35.2)     | <0.001                           |
| Median TIS score (IQR)         | 3 (3–5)         | 2 (1–3)             | 2 (1–3)              | <0.001                           |
| **Epidermal barrier function tests** |                 |                      |                      |                                   |
| Median skin hydration, arbitrary unitsa (IQR) | 39.7 (35.3–46.4) | 45.2 (36.4–56.2)   | 49.2 (41.2–54.6)     | <0.001                           |
| Median TEWL, g/m²/h (IQR)     | 9.4 (8.1–13.6)  | 10.6 (8.5–14.8)    | 11.2 (8.8–15.4)      | 0.1                              |
| **Patient subjective symptoms** |                 |                      |                      |                                   |
| Median DLQI (IQR)              | 6.5 (3–11)      | 3 (2–7)             | 3 (2–7)              | <0.05                            |
| Median POEM (IQR)              | 13 (7–19)       | 8 (4–12)            | 6.5 (3–10)           | <0.001                           |
| Median pruritus (IQR)          | 6 (5–7)         | 4 (2–6)             | 4 (2–6)              | <0.001                           |
| Median insomnia (IQR)          | 2 (0–6)         | 1 (0–5)             | 0 (0–3)              | 0.033                            |

IQR interquartile range, TIS three-item severity, TEWL transepidermal water loss, DLQI Dermatology Life Quality Index, POEM patient-oriented eczema measure

aData available only for 34 patients
warmth sensation after application of the test cream. At week 4, 2 (5%) patients reported pruritus after application of the test product. One patient discontinued the creams at week 3 after he developed worsening of rashes and acneiform papules on the face. There were no other serious adverse events noted.

Patient Adherence and Evaluation

At the end of the study period, 23 (57.5%) of the subjects rated the study cream as excellent or very good, 13 (32.5%) rated it as good and the remaining 4 (10%) rated it as fair. The majority (82.5%) of subjects liked the cream and reported that it improved dryness, provided symptom relief and improved skin texture.

Treatment compliance was assessed by the physician; 27 (67.5%) patients were reported to have excellent compliance, 11 (27.5%) moderate compliance and 2 (5%) poor compliance.

There was a wide variation in the total quantity of study cream used with a mean quantity of 94 g (range 12–396 g, n = 34). There was no difference in the amount used by adults or children. No correlation between the quantity of cream used and the improvement in objective SCORAD during the study period was found.

Prior to study inclusion, all participants used topical corticosteroids. At the final follow-up, 5 (12.5%) subjects had discontinued the use of topical corticosteroids.

DISCUSSION

This prospective open-label clinical trial found that the use of a pseudoceramide moisturizer was effective in improving disease severity, stratum corneum hydration, itch scores and quality of life indices in both pediatric and adult patients with mild or moderate AD. After a 4-week use of the pseudoceramide moisturizer, there was improvement in objective and total SCORAD, TIS, DLQI and POEM scores, which was statistically significant. This is in agreement with previous studies which showed that the use of “physiologic” ceramide moisturizers was effective in improving disease severity, decreasing steroid use and preventing disease flares [11, 12, 31]. This underscores the importance of long-term skin barrier repair in the maintenance therapy of AD [32, 33].

While SC hydration improved significantly, it was interesting that the authors did not find any significant difference for TEWL measurements. Standardization of TEWL measurements can be technically difficult and similar paradoxical findings have been reported in other moisturizer studies [13, 31, 34, 35]. Furthermore, SC hydration is a more sensitive measure of the skin barrier function than TEWL in AD patients [36], as the relationship between TEWL and skin dryness is complex, whereby changes in dryness do not necessarily reflect simultaneous changes in TEWL [37].

The pseudoceramide moisturizer was safe and well tolerated with only 5% of patients reporting pruritus after application. Only 1 patient discontinued with the moisturizer shortly before the end of the study because of a facial rash. It is well established that topical applications, including placebo creams, can cause a transient itch or stinging [38, 39]. In general, the cream was very well tolerated and the majority of patients had positive opinions regarding the efficacy and cosmetic acceptability of the creams. On average, 94 g of the study cream was used during the whole study period. This may be considered low, but it is noted that subjects were only provided with one 72 g tube of study cream every 2 weeks. Despite a smaller body surface area, children were found to have used the same amount of study cream as adult subjects.
This study had several limitations, namely, the small study size, non-blinded design, short duration and the lack of a control arm. The authors also did not obtain information on the exact amount of pseudoceramide moisturizer or topical corticosteroids used over specific affected areas.

CONCLUSION

This study showed that the regular use of a pseudoceramide-containing moisturizer was effective and safe as maintenance therapy in mild-to-moderate AD patients. Further additional, larger comparative trials against placebo creams or “standard” non-lipid-based moisturizers would be needed to further clarify the exact contributory role of lipid-based moisturizers in AD therapy.

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Conflict of interest. AC Seghers, SC Cai, MSL Ho, YC Giam, L Tan, CM Grönhagen and MBY Tang declare no conflicts of interest.

Compliance with ethics. This study was approved by the institution’s Domain Specific Review Board. All procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000 and 2008. Written informed consent was obtained from all patients or their caregivers.

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